

# Are decreased serum Maresin 1 levels predictive of cholangiocarcinoma?

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## ABSTRACT

**Aims:** Cholangiocarcinoma (CC) is a rare form of adenocarcinoma originating from the epithelial cells of the biliary tract. Chronic inflammation is known to be a risk factor for this tumor. The present study aimed to investigate whether serum levels of Maresin 1 (MaR1) (a macrophage-derived anti-inflammatory lipid mediator) were associated with the presence of benign biliary disease (BBD) or CC.

**Methods:** The study was conducted with 104 participants, including 42 patients with CC, 32 patients with BBD, and 30 volunteers without any hepatobiliary pathology. Blood samples were taken from each participant, and serum MaR1 levels were measured with enzyme-linked immunosorbent assay kits.

**Results:** Serum MaR1 levels were significantly lower in the CC and BBD groups compared to controls ( $p < 0.001$ , for both); however, there was no significant difference between the CC and BBD groups in terms of MaR1 level ( $p > 0.05$ ). The cancer antigen (CA) 19-9 and carcinoembryonic antigen (CEA) values of the CC group were found to be significantly higher than the BBD and control groups ( $p < 0.001$ , for both). Although MaR1 was found to have diagnostic value in differentiating patients with CC or BBD from controls, it had no value in distinguishing CC from BBD; whereas CA19-9 and CEA had significant discriminatory power.

**Conclusion:** Decreased serum MaR1 level may predict inflammation in hepatobiliary pathologies such as CC and BBD; however, it cannot be used to discriminate CC from BBD, and classical cancer markers such as CA19-9 and CEA appear to retain superiority in this respect.

**Keywords:** Cholangiocarcinoma, benign biliary disease, Maresin 1

## INTRODUCTION

Cholangiocarcinoma (CC) is an aggressive malignancy from any part of the biliary tract. It has become the second most frequent primary liver cancer in the last decades.<sup>1</sup> CC generally has a poor prognosis, with 5-year survival rates of 30–40% after surgical treatment.<sup>2</sup> Diseases that cause chronic biliary inflammation, such as *Clonorchis sinensis* infections or primary sclerosing cholangitis, are known to be predisposing factors and predict poor prognosis.<sup>3</sup> Inflammation is a necessary process for survival, but repetitive cycles of inflammatory insult or chronic inflammation may lead to tissue fibrosis and DNA mutations which are early steps for carcinogenesis. Various mediators play a role in the resolution of inflammation, and some of these specific mediators are called specialized pro-resolving mediators (SPMs). Decreased levels of such mediators are thought to give rise to unresolved and chronic inflammation, thereby triggering the formation of carcinogenesis with the increase of pro-inflammatory cytokines.<sup>4</sup> Furthermore, since tumorigenesis is closely

related to chronic inflammatory processes, the antitumor activity of SPMs has become a focus of interest in recent studies.<sup>5-7</sup>

Maresin 1 (MaR1) is a macrophage-derived SPM synthesized from docosahexaenoic acid, a form of polyunsaturated fatty acid (PUFA), which exerts anti-inflammatory and cytoprotective effects by stimulating anti-inflammatory macrophages selectively and by inhibiting neutrophil infiltration, generation of reactive oxygen species and expression of inflammatory cytokines.<sup>5,8,9</sup> Previous studies indicate that maresins have a vital role in reversing carcinogenesis in the early stages, and other researchers have shown that tumor cells have decreased amounts of PUFA-related compounds including maresins.<sup>10,11</sup> Based on these data, we hypothesized that serum levels of MaR1 may be associated with the risk of diseases demonstrating chronic inflammation, including cancer, and also may be used as a

marker for the early diagnosis of some types of cancer that are difficult to diagnose. To the best of our knowledge, there are currently no studies that have investigated the relationship between MaR1 and CC.

In the present study, we investigated the serum MaR1 levels in patients with CC, patients with benign biliary disease (BBD), and healthy volunteers to identify the role of MaR1 in the pathogenesis of CC and its potential to be used as a marker for CC diagnosis.

## METHODS

### Ethics

Study participation was approved by the Clinical Researches Ethics Committee of Kırıkkale University Faculty of Medicine (Date: 24.04.2021, Decision No: 05/05). All procedures were conducted in accordance with the principles of the Declaration of Helsinki and its subsequent amendments or comparable ethical standards.

### Study Design and Population

This study was conducted with 42 patients with CC and 32 patients with BBD who applied to the Gastroenterology Outpatient Clinic of Kırıkkale University Faculty of Medicine. The BBD group included patients with choledocholithiasis, benign biliary stricture, gallbladder stone, and Mirizzi syndrome, and no cases with acute inflammatory conditions such as acute cholangitis were present. This minimizes the likelihood of acute inflammation acting as a confounding factor on MaR1 levels. Also, 30 healthy volunteers who were admitted to internal medicine outpatient clinics for routine controls between May and December 2021 were included in the study. The study was observational and prospective in design and was not registered as a clinical trial. Patients younger than 18 years of age, those with any systemic or metabolic disease (diabetes mellitus, chronic renal disease, collagen tissue disease, etc.), other malignancies, patients under chronic immunosuppressive or steroid treatment, those with chronic inflammatory diseases or a history of organ transplantation, and subjects who refused participation were excluded from the study. The healthy volunteer group comprised individuals aged 18 years or older who did not have any acute or chronic diseases.

Serum levels of MaR1 and other laboratory outcomes were evaluated comparatively between the two study groups (42 patients with CC and 32 patients with BBD) and one control group (30 healthy volunteers).

### Laboratory Analysis

After at least 12 hours of fasting, 2 ml venous blood samples were drawn from all participants. Serum samples were separated by centrifugation at 5000 rpm for 5 minutes and were transferred to sterile Eppendorf tubes and stored in a deep freezer at  $-80^{\circ}\text{C}$ .

C-reactive protein (CRP), aspartate transaminase, alanine transaminase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), fasting plasma glucose, total bilirubin, albumin, and creatinine were studied using Roche Cobas® c501 brand device with original Roche diagnostic kits.<sup>12</sup> Hemogram parameters (hemoglobin, white blood cell, platelet, neutrophil, lymphocyte, etc.) were studied

by flow cytometric impedance method in an automatic complete blood count device (Mindray BC 6800, Shenzhen, China). Cancer antigen (CA) 19-9 and carcinoembryonic antigen (CEA) levels were studied by chemiluminescence using Cobas® e601 brand device. Serum Maresin 1 levels were measured using a Human MaR1 enzyme-linked immunosorbent assay (ELISA) kit (Sunred Biotechnology Company, Shanghai, China) in accordance with the manufacturer's instructions. The optical density at 450 nm was quantified spectrophotometrically with a CLARIOstar PLUS device (BMG Labtech, Germany). Test results were expressed in pg/ml. The measurement range of the kit was 7.5–2000 pg/ml, with a sensitivity of 7.247 pg/ml. The intra-assay coefficient of variation (CV) was <10%, and the inter-assay CV was <12% as reported by the manufacturer.

### Statistical Analysis

The IBM SPSS 23.0 package program (IBM Corp., Armonk, NY) was used for all analyses, and a significance threshold of 0.05 (p-value) was set. The normality of data distribution was assessed using the Shapiro–Wilk test. Depending on the distribution pattern, parametric or non-parametric tests were applied. Descriptive statistics were presented as frequency (n) and percentage (%) for categorical variables, and, for normally distributed continuous variables, descriptive data were given with mean±standard deviation (SD) values, while median (min-max) values were used for continuous variables without normal distribution. Categorical variable distributions were compared with Fisher's Exact or Pearson's Chi-square tests. The Kruskal-Wallis's test was used in the non-parametric comparison of the continuous variables between groups, and the Bonferroni correction was used as the post hoc test for significance. One-way ANOVA was used to compare three groups when the assumption of normal distribution was met, and for pairwise analyses, the Tukey HSD test was used when homogeneity of variance was met, while the Dunnett T3 test was used when it was not met. Receiver operating characteristic (ROC) analysis was performed to assess the diagnostic performance of biochemical parameters and to determine cut-off values. The results were presented with the area under curve (AUC), cut-off points, sensitivity, and specificity values, with 95% confidence intervals (CIs).

### Sample Size and Power Analysis

A priori sample size estimation was performed using G\*Power version 3.1. Assuming an expected AUC of 0.75 and a significance level of  $\alpha=0.05$ , a minimum of 50 participants in total (CC and BBD groups combined) was required to achieve 80% statistical power. In our study, with 42 patients in the CC group and 32 in the BBD group (n=74 in total), the achieved power was calculated as 97.9%, indicating that the study was adequately powered.

## RESULTS

The mean age of the participants was  $71.48\pm 11.14$  years in the CC group,  $64.81\pm 13.45$  years in the BBD group, and  $61.47\pm 8.74$  years in the control group. The mean ages of the CC and BBD groups were significantly higher than the control group (p=0.001). The frequency of male patients in the CC and BBD groups (54.8% and 59.4%; respectively) was higher than the control group (26.7%) (p=0.019). When biochemical and hemogram parameters were evaluated relative to control

values, we found that fasting blood glucose, CRP, AST, ALT, ALP, GGT, and total bilirubin levels were significantly higher, while platelet and MaR1 levels were significantly lower in the CC and BBD groups ( $p < 0.05$  for all). In addition, in the CC group, ALT and hemoglobin levels were significantly lower, and ALP, CEA, and CA19-9 levels were significantly higher compared to patients in the BBD group ( $p < 0.05$  for all) (Table 1).

ROC analysis was performed to determine the discriminative performance of MaR1 to distinguish CC and BBD patients from controls, while MaR1, CEA, and CA19-9 values were assessed for their role in distinguishing CC patients from those with BBD (Table 2).

The discriminative performance of MaR1 values was found to be high in identifying CC patients from controls (AUC=0.880, 95% CI: 0.782-0.945;  $p < 0.001$ ) (Figure 1a) and BBD patients from controls (AUC=0.826, 95% CI: 0.708-0.910;  $p < 0.001$ ) (Figure 1b). For discrimination of CC from controls, the optimal cut-off value was  $\leq 467.94$ , with 90.48% sensitivity and 73.33% specificity. For discrimination of BBD from controls, the optimal cut-off value was  $\leq 415.19$ , with 75% sensitivity and 76.67% specificity. MaR1 values were not found to have significant value in distinguishing patients with CC from those with BBD ( $p > 0.05$ ) (Figure 1c).

The discriminative performance of CEA and CA19-9 values were found to be high in terms of distinguishing CC patients from those with BBD (AUC=0.807, 95% CI: 0.698-0.889;  $p < 0.001$  for CEA (Figure 2a), and AUC=0.922, 95% CI: 0.836-0.971;  $p < 0.001$  for CA19-9 (Figure 2b).

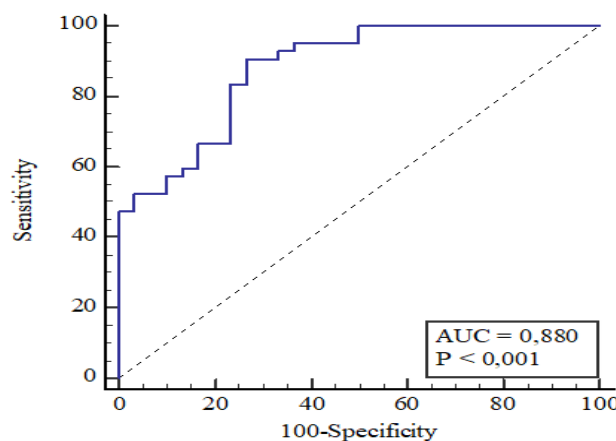


Figure 1a. ROC curve for MaR-1 in differentiating CC from control  
ROC: Receiver operating characteristic, MaR1: Maresin 1, CC: Cholangiocarcinoma, AUC: Area under the curve

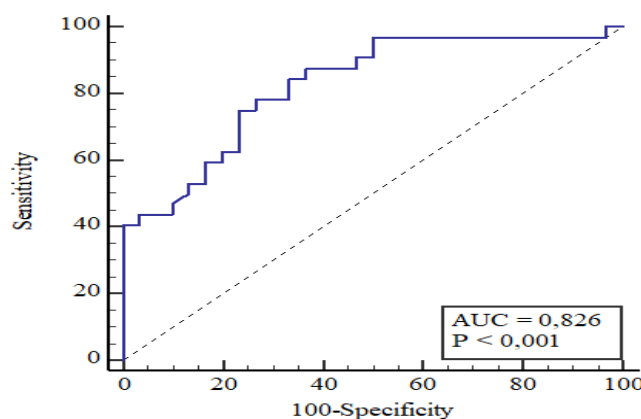


Figure 1b. ROC curve for MaR-1 in differentiating BBD from control  
ROC: Receiver operating characteristic, BBD: Benign biliary disease, AUC: Area under the curve

Table 1. Demographic and clinical characteristics of patients according to study groups

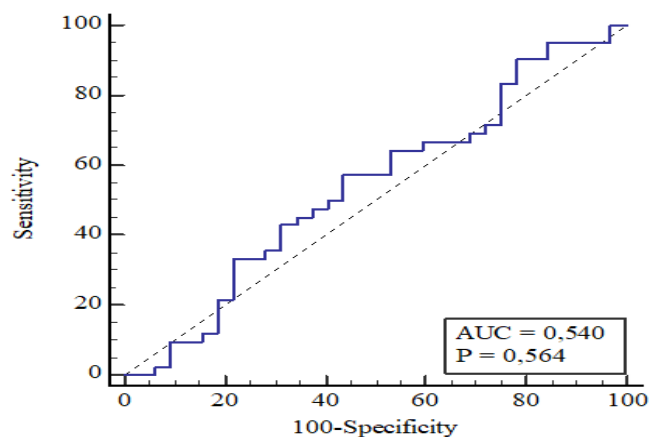
	CC (n:42)	BBD (n:32)	Control (n:30)	p
FBG, mg/dl	119.5 (91-132) <sup>a</sup>	121 (104-158) <sup>a</sup>	98 (92-112) <sup>b</sup>	0.001
CRP, mg/L	36 (14-69) <sup>a</sup>	14.25 (3.95-59.05) <sup>a</sup>	4.06 (2.5-8) <sup>b</sup>	0.001
AST, IU/L	73.5 (34-130) <sup>a</sup>	108 (44.5-201.5) <sup>a</sup>	18 (15-22) <sup>b</sup>	0.001
ALT, IU/L	53 (30-135) <sup>a</sup>	122.5 (49.5-297.5) <sup>b</sup>	16 (13-26) <sup>c</sup>	0.001
ALP, IU/L	384 (203-610) <sup>a</sup>	227.5 (104-336) <sup>b</sup>	75.5 (55-93) <sup>c</sup>	0.001
GGT, IU/L	434.5 (157-738) <sup>a</sup>	257.5 (99.5-539) <sup>a</sup>	47 (26-65) <sup>b</sup>	0.001
HGB, g/dl	11.76±1.54 <sup>a</sup>	13.27±2.45 <sup>b</sup>	14.16±1.21 <sup>b</sup>	0.001
WBC, x10 <sup>9</sup> /L	8.25 (6.87-10.1)	7.95 (6.55-12.4)	7.56 (5.93-8.5)	0.257
Platelet, x10 <sup>9</sup> /L	236 (196-280) <sup>a</sup>	233.5 (181-282) <sup>a</sup>	270.5 (235-297) <sup>b</sup>	0.039
CEA, ng/ml	5 (2.57-15)	2 (1-3.38)	-	0.001
CA19-9, U/ml	230.65 (102-539)	10.3 (5.38-22.8)	-	0.001
T.bil, $\mu$ mol/L	6 (1-12) <sup>a</sup>	2.6 (1.15-5.75) <sup>a</sup>	0.65 (0.51-0.9) <sup>b</sup>	0.001
MaR1, pg/ml	326.52 (243.02-423.88) <sup>a</sup>	343.24 (256.25-426.56) <sup>a</sup>	551.66 (437.48-746.53) <sup>b</sup>	0.001

Data are given as mean±standard deviation or median (min-max) for continuous variables according to the normality of distribution. <sup>a,b,c</sup>: Different exponential letters in the same row indicate statistically significant differences between groups. ALT: Alanine transaminase, ALP: Alkaline phosphatase, AST: Aspartate transaminase, BBD: Benign biliary disease, CC: Cholangiocarcinoma, CEA: Carcinoembryonic antigen, CRP: C-reactive protein, FBG: Fasting blood glucose, GGT: Gama-glutamyl transferase, HGB: Hemoglobin, MaR1: Maresin 1, T.bil: Total bilirubin, WBC: White blood cell

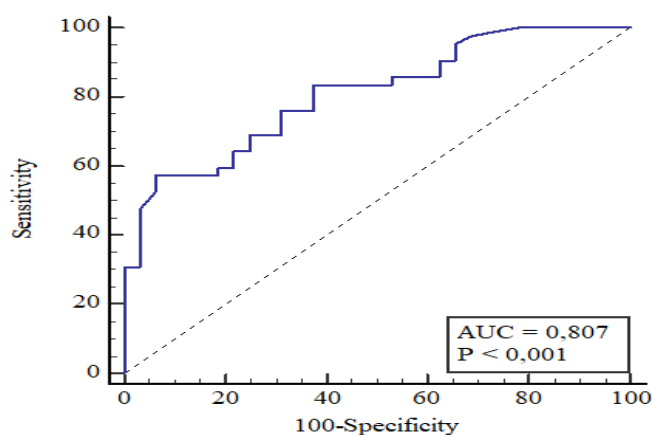
Table 2. ROC analysis for MaR1, CEA and CA19-9

	AUC (95% CI)	p	Cut-off	Sensitivity	Specificity
MaR1 (CC/control)	0.880 (0.782-0.945)	<0.001	$\leq 467.94$	90.48%	73.33%
MaR1 (BBD/control)	0.826 (0.708-0.910)	<0.001	$\leq 415.19$	75.00%	76.67%
MaR1 (CC/BBD)	0.540 (0.420-0.657)	0.564	-	-	-
CEA (CC/BBD)	0.807 (0.698-0.889)	<0.001	>4.22	57.14%	93.75%
CA19-9 (CC/BBD)	0.922 (0.836-0.971)	<0.001	>80.20	76.19%	100.00%

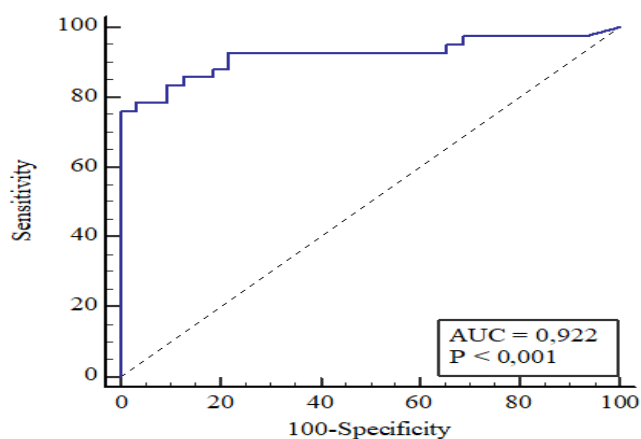
ROC: Receiver operating characteristic, AUC: Area under the curve, BBD: Benign biliary disease, CA: Cancer antigen, CC: Cholangiocarcinoma, CEA: Carcinoembryonic antigen, MaR1: Maresin 1



**Figure 1c.** ROC curve for MaR-1 in differentiating CC from BBD  
 ROC: Receiver operating characteristic, MaR1: Maresin 1, CC: Cholangiocarcinoma, AUC: Area under the curve, BBD: Benign biliary disease



**Figure 2a.** ROC curve for CEA in differentiating CC from BBD  
 ROC: Receiver operating characteristic, CC: Cholangiocarcinoma, AUC: Area under the curve, BBD: Benign biliary disease, CEA: Carcinoembryonic antigen



**Figure 2b.** ROC curve for CA19-9 in differentiating CC from BBD  
 ROC: Receiver operating characteristic, CC: Cholangiocarcinoma, AUC: Area under the curve, BBD: Benign biliary disease, CA: Cancer antigen

## DISCUSSION

Although rare, CC is a malignancy with a poor prognosis partly because diagnosis is often delayed with current diagnostic methods. Definitive diagnosis is usually based on imaging techniques and tissue biopsy. Some tumor markers, especially CEA and CA19-9, have been used for tumor screening –especially in risk groups– and for the follow-up of the disease.<sup>13</sup> However these markers were shown to have variable sensitivity and specificity in different studies, and therefore, their usefulness for this purpose cannot always

be generalized.<sup>14</sup> New sensitive and specific algorithms are needed to enable early diagnosis and to improve treatment success. In the present study, serum MaR1 levels in patients with CC and BBD were investigated for the first time, and levels were found to be significantly lower compared to healthy subjects. However, it was determined that CEA and CA19-9 levels were relatively better in the differential diagnosis of CC patients compared to MaR1–which does not appear to have the potential to distinguish CC from BBD.

It is known that prolonged or recurrent low-grade inflammation plays an important role in the pathophysiology of various malignancies and other diseases via mechanisms of oxidative stress, necrosis, fibrosis, and DNA damage, indicating the criticality of the balance between the development and resolution of inflammation which unanimously remains as a topic of interest.<sup>15-21</sup> As mentioned previously, endogen chemicals that contribute to a swift resolution of acute inflammation are called SPMs.<sup>22</sup> MaR1 is a member of the SPM family and has been suggested to inhibit proinflammatory cytokines, thereby limiting chronic inflammation and potentially preventing inflammation-induced proliferation of cancer cells. For instance, in a study conducted by Li et al.,<sup>23</sup> the effects of MaR1 on liver damage (induced by intraperitoneal carbon tetrachloride injection) were investigated in an experimental mice model. MaR1 was shown to alleviate liver damage, decrease inflammatory mediators, and increase the antioxidative mediators. In a similar study by Fang et al.,<sup>24</sup> serum MaR1 levels in patients with non-alcoholic fatty liver disease were found to be significantly lower than in healthy individuals. In another study, conducted with a mice model of ulcerative colitis (induced by dextran sulfate sodium), the disease activity index, macrophage infiltration, and oxidative enzyme activity were found to have decreased after MaR1 treatment.<sup>25</sup> Vatnick et al.<sup>26</sup> demonstrated that maresins inhibit the growth of primary breast cancer cells by stimulating the apoptotic effect of macrophages and increasing endogenous anti-inflammatory cytokines. Also, it has been reported that omega-3 PUFA treatment causes tumor regression by stimulating apoptosis in gastric cancer cells, which may show an underlying relationship with MaR1 since this mediator is synthesized from PUFAs.<sup>27</sup> Consistently, the study by Varol et al.<sup>28</sup> was the one that demonstrated the role of MaR1 alterations in the pathogenesis of chronic pancreatitis, further supporting the relevance of MaR1 in inflammation-driven diseases. Based on these data, we hypothesized that low serum MaR1 levels could serve as a marker for the early detection of CC. However, the findings of our study only partially supported this hypothesis. While serum MaR1 levels clearly distinguished CC patients from healthy individuals, they failed to differentiate CC patients from those with BBD. Although we excluded acute cholangitis and infectious conditions from the BBD group, non-infectious factors such as gallstone-related obstruction, bile stasis, and chronic mucosal irritation may have triggered persistent inflammatory responses in these patients. This underlying non-infectious inflammatory background likely contributed to the similarities observed between the CC and BBD groups. Therefore, our results suggest that serum MaR1 levels alone may be insufficient to discriminate between diseases that share overlapping chronic inflammation–driven pathological mechanisms.

In our study, some other related biochemical parameters were also examined, including AST, ALT, ALP, and GGT (which can mirror hepatobiliary damage), CRP and WBC (markers of inflammation), total bilirubin (associated with anabolic liver functions), CEA and CA19-9. The levels of many of these parameters were found to be significantly elevated in patients with CC compared to the other two groups. Similarly, previous studies have reported that these parameters increase to a level that has diagnostic value in CC patients. Gül et al.<sup>29</sup> compared CA19-9 levels in CC patients, BBD patients, and healthy participants, and showed significantly higher levels of the CA19-9 tumor marker in CC patients. Conversely, in another study, the CA19-9 and CEA levels were measured to be considerably elevated in patients with obstructive jaundice and hepatolithiasis; therefore, they concluded that the 'tumor marker' utility of these parameters was questionable in several conditions.<sup>21</sup> Although many different results have been presented in various studies, CEA and CA19-9 are reported to have sensitivity and specificity values around 70% and 90% for the identification of CC based on BBD.<sup>30</sup> In an earlier study by Ramage et al.,<sup>31</sup> an index score derived from serum CEA and CA19-9 levels was reported to detect CC development with an accuracy of 86% among a group of patients with BBD. We also found similar sensitivity and specificity for CEA and CA19-9 in the discrimination of CC from BBD. Therefore, taken together, these results further support our notion that MaR1 levels provide unsatisfactory results in this context.

### Limitations

One of the main limitations of our study is that it was conducted in a single center with a relatively limited number of patients. In addition, homogeneity in terms of age and sex could not be achieved between the control and patient groups, which may have introduced potential confounding effects in the interpretation of MaR1 levels. The possible effects of age and sex on MaR1 levels were not specifically analyzed in our study, and this should be considered as a potential limitation. MaR1 measurements were performed at a single time point only, and therefore intra-individual variability of biomarker levels could not be assessed. Moreover, CEA and CA19-9 levels were not measured in the healthy control group due to ethical reasons, which precluded direct comparison with the patient groups. Finally, the potential additional diagnostic value of MaR1 in combination with CA19-9 or CEA was not evaluated. Furthermore, the statistical analyses were limited by the sample size, and therefore the generalizability of the findings may be restricted. These limitations should be taken into account when interpreting the results.

### CONCLUSION

As a result, serum MaR1 levels were found to be significantly lower in the CC and BBD groups compared to the control group. MaR1 levels appear to be incapable of distinguishing between CC and BBD, possibly due to the considerable levels of inflammation in patients with BBD. On the other hand, classical cancer markers, CEA and CA19-9, were significantly elevated in the CC group and demonstrated reliability in distinguishing CC from BBD. Accordingly, MaR1 may be a marker to predict inflammation in CC and BBD; however, it does not appear to have a tumor marker value in the differential diagnosis for CC.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

Study participation was approved by the Clinical Researches Ethics Committee of Kırıkkale University Faculty of Medicine (Date: 24.04.2021, Decision No: 05/05).

### Informed Consent

Written informed consent was obtained from all individual participants prior to their inclusion in the study. Participants were fully informed about the study's aims, procedures, potential risks and benefits, and their rights—including the right to withdraw at any time without consequence. All participants voluntarily signed a written informed consent form.

### Peer Review Process

This manuscript was subject to external peer review.

### Conflict of Interest

The authors declare no conflicts of interest related to this study.

### Financial Disclosure

The authors received no financial support for the conduct or publication of this research.

### Author Contributions

Concept: S.K., B.E., Ö.G.; Design: B.E., S.K.; Control: S.K., B.E., Ö.G.; Resources: S.K.; Ü.K., E.T.; Materials: S.K.; Ü.K., E.T.; Data Collection and/or Processing: S.K., B.E., E.T.; Analysis and/or Interpretation: B.E., Ü.K., Ö.G.; Literature Review: S.K., B.E., Ö.G.; Article Writing: S.K., B.E., Ü.K.; Critical review: S.K., B.E., Ö.G.

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