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ORIGINAL ARTICLE

Association of Low Serum Maresin-1 Levels with Hepatocellular Carcinoma in Cirrhotic Liver

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SUMMARY

Background: **Maresin-1 (MaR1) is a macrophage-derived antiinflammatory lipid mediator that negatively regulates oxidative and proinflammatory cytokines and also restores integrity in various tissues after inflammation. Non-resolving inflammation is known to have an important role in the pathogenesis of hepatocellular carcinoma (HCC). The aim of the present study was to evaluate the role of MaR1 in pathogenesis and early diagnosis of HCC.**

Methods: **The study was conducted in 102 participants, including 30 volunteers with no hepatic disease, 39 patients with hepatic cirrhosis, and 33 patients with HCC that developed additionally to cirrhosis. Serum MaR1 levels of all participants were measured by enzyme-linked immunosorbent assay (ELISA).**

Results: **There was a significant difference between the circulating MaR1 levels of the three groups. MaR1 level was found to be significantly lower in the HCC group compared to the cirrhotic group ($p < 0.001$) and in the cirrhotic group compared to the healthy control group ($p < 0.001$). MaR1 level was independently associated with cirrhosis (vs. controls, OR: 0.995, $p = 0.025$) and with HCC (vs. controls, OR: 0.962, $p = 0.035$; and vs. cirrhotic patients, OR: 0.987, $p = 0.006$). ROC analyses demonstrated that MaR1 levels of < 311.66 had 72.73% sensitivity and 100% specificity for HCC differentiation from controls, while a < 428.08 cutoff had 96.97% sensitivity and 38.46% specificity for differentiation from cirrhotic patients.**

Conclusions: **Serum MaR1 levels were significantly decreased in patients with HCC, compared to those with normal or cirrhotic hepatic tissue. Therefore, MaR1 may possibly be a valuable biomarker in the early diagnosis of HCC and in the differential diagnosis of HCC from cirrhosis.**

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KEYWORDS

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INTRODUCTION

Primary liver cancer is the sixth most prevalent type of cancer and the fourth most common cause of cancer-related death worldwide [1]. Hepatocellular carcinoma (HCC) accounts for about 75 - 90% of total liver cancer cases [2,3]. Since the disease is usually asymptomatic in its early stages, diagnosis is delayed in most patients, leading to limited therapeutic options and poor prog-

nosis [4]. Most HCC cases appear on the basis of cirrhosis, as a result of the vicious cycle of inflammation and regeneration in hepatocytes [3,5]. Definitive diagnosis is reliant on histopathologic evaluation [6], since imaging methods such as ultrasonography (USG), computerized tomography (CT), and magnetic resonance imaging (MRI) do not provide sufficient sensitivity in detecting tumors, especially in the presence of cirrhotic background [7,8]. Alpha-fetoprotein (AFP) is a widely used tumor marker for HCC, but its diagnostic value is controversial [8,9]. Therefore, there is a need for reliable markers that can be used in the follow-up of cirrhotic patients and can detect HCC formation in its early stages.

Increasing evidence shows that polyunsaturated fatty acids (PUFAs) have protective effects in several cancers, including liver cancer [10,11]. Maresin-1 (MaR1), a lipid mediator derived from PUFA that is biosynthesized in macrophages, has been demonstrated to have a vital role in inflammation resolution and reverses tissue damage caused by ischemia-reperfusion injury [12] or by metabolic or immunologic hepatic diseases [13,14]. It is suggested to exert its effects by inhibiting the generation of reactive oxygen species and expression of inflammatory cytokines, including interleukins and tumor necrosis factor [10].

As a common result of studies examining the relationship between serum MaR1 levels and diseases caused by inflammatory processes, it was concluded that low serum MaR1 levels are associated with increased risk for such diseases [15,16]. However, there is limited data concerning the role of MaR1 in the development of HCC.

Considering the anti-inflammatory and cytoprotective effects of MaR1, the aim of the present study was to evaluate its role in the pathogenesis of HCC and to identify the potential of this new noninvasive marker in the early diagnosis of HCC.

MATERIALS AND METHODS

Study design and population

This case-control study included 32 patients with HCC and 39 patients with cirrhosis who applied to the Gastroenterology Outpatient Clinic of Kirikkale University Medical Faculty and 30 healthy volunteers who applied to the Internal Medicine Outpatient Clinic between May 2021 and September 2021. Approval for the study was obtained from the Clinical Research Ethics Committee of Kirikkale University Medical Faculty (date: April 29, 2021, decision No. 05/09). Patients younger than 18 years, those with other liver diseases or other organ malignancy, and subjects who did not approve participation with the informed consent forms were excluded from the study.

After at least 12 hours of fasting, 2 mL venous blood samples were taken from all participants. Serum samples separated by centrifugation of blood at 1,500 × g for 10 minutes were transferred to sterile Eppendorf tubes and stored at -80ºC until measurements.

Laboratory analysis

Fasting plasma glucose, C-reactive protein (CRP), aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), total bilirubin, albumin, and creatinine were studied using a Roche Cobas® C501 brand device using the original Roche diagnostic kits. 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). Serum AFP levels were studied via the chemiluminescence method. Serum MaR1 levels were measured by using a human maresin-1 ELISA kit according to the manufacturer's instructions (SinoGeneClon Biotech Co., Ltd., Hangzhou, China, catalog no. SG-15235).

Statistical analysis

Analyses were performed with the IBM SPSS, version 23.0, package program (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as frequency and percentage for categorical variables, and as mean ± standard deviation (SD) or median (min - max) values for continuous variables. The assumption of normality was checked with the Shapiro-Wilk test. The Fisher's exact Test or Pearson's chi-squared test was used to analyze the two groups in terms of categorical variable distributions. The Mann-Whitney U test was used for 2-group comparisons of quantitative variables that did not fit normal distribution, and the Kruskal-Wallis test was used for the comparison of > 2 groups. One-way ANOVA was used in the comparison of three groups when the assumption of normal distribution was met, and pairwise comparisons were performed with the Dunnett T3 test when homogeneity of variance was met, while the Tukey HSD test was used when not. Receiver operating characteristics (ROC) analysis was performed to assess the diagnostic value of biochemical parameters, and the Youden J index was used to determine cutoff points. Results were presented with area under the curve (AUC), cutoff points, sensitivity, and specificity values. Multivariable logistic regression analysis was performed to determine independent risk factors associated with cirrhosis and HCC in patients, and the results were presented with odds ratio (OR) and 95% confidence intervals (CI). Two-tailed p-values of less than 0.05 were considered statistically significant.

RESULTS

The percentage of male patients was 75.8% in the HCC group, 56.4% in the cirrhosis group, and 30% in the control group. The male/female ratio was found to be significantly higher in the HCC group than in the control group ($p = 0.001$). The mean age was 67.21 ± 7.86

Table 1. Biochemical parameters of the study groups.

Variables	HCC (n = 33)	Cirrhosis (n = 39)	Control (n = 30)	p-value
CRP (mg/L)	20 (0.01 - 150) [a]	4 (0.1 - 144) [b]	4.06 (1 - 20) [b]	0.005
AST (IU/L)	65 (14 - 1,273) [a]	26 (12 - 164) [b]	17 (10 - 31) [c]	< 0.001
ALT (IU/L)	42 (9 - 460) [a]	21 (7 - 161) [b]	16 (9 - 51) [b]	< 0.001
ALP (IU/L)	215 (36 - 842) [a]	109 (60 - 263) [b]	80 (59 - 128) [b]	< 0.001
GGT (IU/L)	108 (18 - 812) [a]	33 (12 - 589) [b]	34.5 (11 - 72) [b]	< 0.001
Leukocyte	7,590 (1,020 - 29,620) [a]	4,540 (1,720 - 31,040) [b]	7,450 (4,000 - 11,000) [a]	< 0.001
Total bilirubin (mg/dL)	1.2 (0.4 - 42) [a]	0.89 (0.46 - 17) [b]	0.75 (0.3 - 2) [b]	0.003
Albumin*	3.36 ± 0.81 [a]	3.83 ± 1.01 [b]	4.59 ± 0.36 [c]	< 0.001
Creatinine	1 (0.1 - 9) [a]	0.9 (0.35 - 3.1) [a]	0.68 (0.39 - 1.37) [b]	0.006
AFP (ng/mL)	53 (1 - 1,210) [a]	3.4 (0.9 - 58) [b]	2.55 (1.19 - 30.52) [b]	< 0.001
MaR1 (pg/mL)	285.78 (101.41 - 538.57) [a]	345.7 (202.15 - 949.26) [b]	517.83 (320.06 - 1,238.86) [c]	< 0.001

Data are given as mean ± standard deviation or median (min - max) for continuous variables according to normality of distribution.
Different exponential letters in the same row indicate statistically significant difference between groups.
ALT - alanine transaminase, AST - aspartate transaminase (AST), ALP - alkaline phosphatase, AFP - alpha-fetoprotein, CRP - C-reactive protein, GGT - gamma-glutamyl transferase, MaR1 - maresin-1.

Table 2. Determination of independently-associated factors with cirrhosis and HCC via multivariable regression (forward selection method).

Group comparison	Model	Parameter	OR (95% GA)	Wald	p
Cirrhosis vs. control	Model 1	Leukocyte	0.956 (0.927 - 0.986)	8.343	0.004
		MaR1	0.995 (0.990 - 0.999)	5.023	0.025
		AFP	1.122 (0.960 - 1.311)	2.096	0.148
		Total bilirubin	1.764 (0.974 - 3.193)	3.511	0.061
		ALP	1.051 (1.010 - 1.093)	5.967	0.015
HCC vs. control	Model 2	ALP	1.068 (0.986 - 1.156)	2.621	0.105
		MaR1	0.962 (0.929 - 0.997)	4.430	0.035
HCC vs. cirrhosis	Model 3	Leukocyte	1.115 (0.992 - 1.253)	3.338	0.068
		CRP	1.008 (0.984 - 1.033)	0.383	0.536
		MaR1	0.987 (0.978 - 0.996)	7.56	0.006
		AFP	1.035 (0.978 - 1.096)	1.398	0.237
		ALT	1.000 (0.970 - 1.032)	0.001	0.975
		GGT	1.008 (0.992 - 1.025)	0.983	0.322
		ALP	1.006 (0.992 - 1.020)	0.645	0.422

ALT - alanine transaminase, AST - aspartate transaminase, ALP - alkaline phosphatase, AFP - alpha-fetoprotein, CRP - C-reactive protein, GGT - gamma-glutamyl transferase, MaR1 - maresin-1.

years in the HCC group, 62.85 ± 11.03 years in the cirrhosis group, and 60.17 ± 6.98 years in the control group. The mean age of the HCC group was statistically higher than of the control group ($p = 0.009$). Biochemical parameters of the groups are given in Table 1. Accordingly, the CRP, AST, ALT, ALP, GGT, total bilirubin, and AFP levels of the HCC group were significantly higher compared to the cirrhosis and control groups ($p < 0.001$). Albumin and MaR1 levels of patients with HCC were significantly lower compared to the cirrhosis and control groups ($p < 0.001$).

Factors independently associated with cirrhosis and

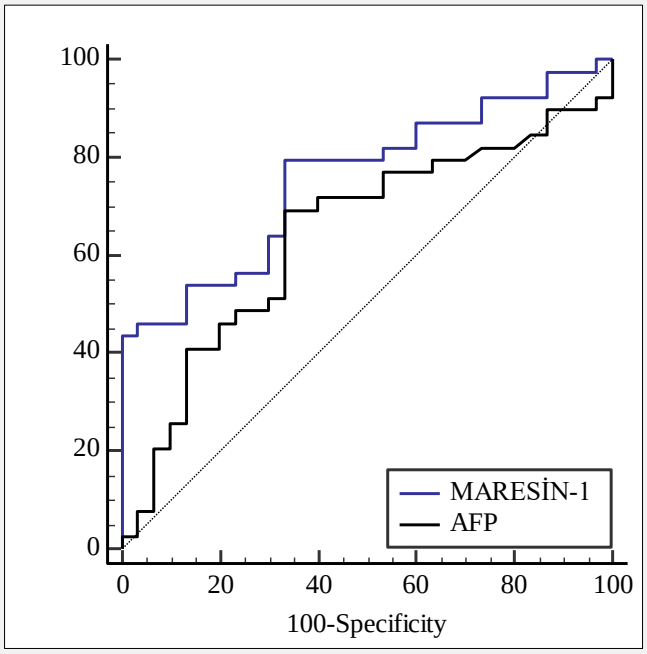

Figure 1. ROC curve for MaR-1 and AFP in differentiating the cirrhosis patients from the controls.

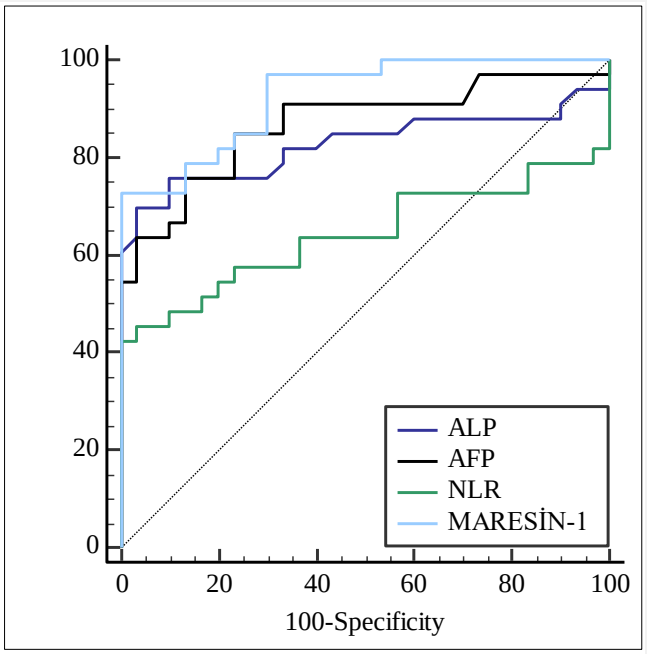

Figure 2. ROC curve for NLR, MaR1, AFP, and ALP in differentiating HCC patients from controls.

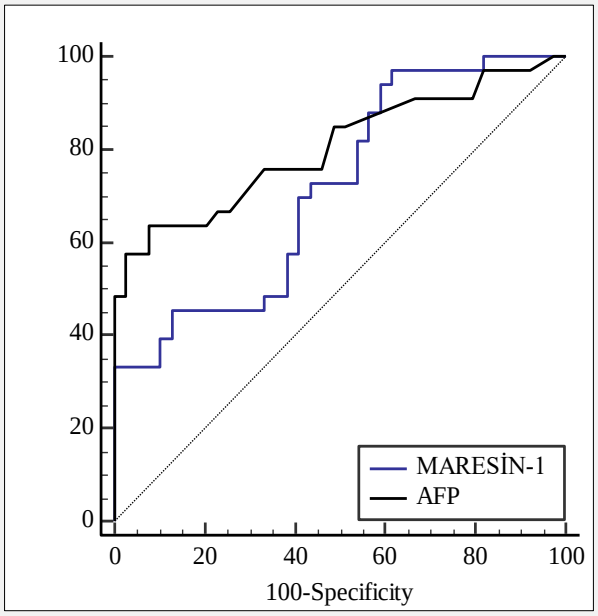

Figure 3. ROC curve for MaR-1 and AFP in differentiating HCC from cirrhosis.

HCC were examined by multivariable logistic regression analysis (Table 2). In model 1, cirrhosis-related factors in cirrhosis patients relative to controls were investigated by controlling for age and gender. Accordingly, decreased leukocytes (OR: 0.956, 95% CI: 0.927 - 0.986; p = 0.004), decreased MaR1 (OR: 0.995, 95% CI: 0.990 - 0.999; p = 0.025), and increased ALP (OR: 1.051, 95% CI: 1.01 - 1.093; p = 0.043) levels were found to be related to increased risk for cirrhosis. In model 2, HCC-related factors relative to controls were investigated by forward selection method by controlling for age and gender. Accordingly, decreased MaR1 levels were found to be associated with increased risk for HCC (OR: 0.962, 95% CI: 0.929 - 0.997; p = 0.035). In model 3, HCC-related factors were investigated relative to cirrhosis by controlling for age and gender. Accordingly, the risk of HCC was found to be increased when MaR1 levels decreased in patients with cirrhosis (OR: 0.987, 95% CI: 0.978 - 0.996; p = 0.006).

The performance of the variables in differentiating the control, cirrhosis, and HCC groups was evaluated by ROC analysis. The AUC values assessing the performance of MaR1 and AFP variables in differentiating cirrhosis from controls were found to be similar (Figure 1) (MaR1 AUC: 0.757, 95% CI: 0.639 - 0.852; p < 0.001 and AFP AUC: 0.641, 95% CI: 0.517 - 0.753; p = 0.040). Respective sensitivity and specificity values were calculated as 79.49% and 66.67% for MaR1 with a < 477.23 cutoff point and as 67.23% and 66.67% for AFP with a > 2.77 cutoff point. Next, the performance of the NLR, ALP, MaR1, and AFP variables in differentiating HCC patients from controls was evaluated. Respective sensitivity and specificity values were calculated as 72.73% and 100% for MaR1 with a < 311.66 cutoff point (AUC: 0.926, 95% CI: 0.832 - 0.977; p < 0.001) and as 75.76% and 86.67% for AFP with a > 4.41 cutoff point (AUC: 0.867, 95% CI: 0.757 - 0.939; p < 0.001) (Figure 2). Finally, the ROC analyses of MaR1 and AFP in differentiating HCC patients from those with cirrhosis are presented in Figure 3. MaR1 and AFP values were effective in differentiating HCC from cirrhosis (AUC: 0.716, 95% CI: 0.597 - 0.816; p < 0.001 and AUC: 0.803, 95% CI: 0.692 - 0.887, p < 0.001, respectively). Sensitivity and specificity values were calculated as 96.97% and 38.46% for MaR1 with a < 428.08 cutoff point and as 63.64% and 92.31% for AFP with a > 8.16 cutoff point.

DISCUSSION

Most patients with HCC have underlying cirrhosis, which may prevent early diagnosis and effective treatment. It is urgently necessary to develop new sensitive and specific algorithms to distinguish HCC from cirrhosis. In the present study, serum MaR1 levels in cirrhotic patients with HCC were found to be significantly lower compared to cirrhotic patients without HCC and healthy

subjects. The potential of MaR1 as an early marker for HCC was evaluated for the first time in this study, and it was observed to have satisfactory diagnostic performance.

Low-grade chronic inflammation is known to be one of the factors associated with the development and/or progression of malignancies. Acute inflammation is a protective response of the tissue against deleterious external factors, but it must be physiologically terminated by immunological mechanisms, including specialized pro-resolving mediators (SPMs), within a certain time [17]. Prolonged or non-resolved inflammation increases the risk of necrosis or fibrosis in the tissue and may also lead to genetic alterations, all of which might be associated with cancer development [18]. The anticancer actions of SPMs, possibly through targeting of tumor cells, alterations in tumor microenvironment, and effects on pro-cancerous lesions, have been demonstrated by previous studies [19,20]. Kyu Lim et al. showed with *in vitro* studies that PUFA, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) derivatives prevent HCC development by inhibiting COX-2 and beta-catenin pathways [21]. These molecules were also shown to induce apoptosis of tumor cells in similar studies [22]. In relation, Nassar et al. demonstrated that tumor cells have decreased amounts of PUFAs [23]. In a study conducted by Leon et al., it was shown that the expression of inflammatory mediators such as TNF-α and IL-1β in the colon mucosa decreased with application of MaR1 treatment to mice with diet-induced obesity. In the aforementioned study, MaR1 ameliorated the inflammatory state in the colonic mucosa and partially compensated the changes in the gut microbiota caused by obesity [24]. A recent cross-sectional study conducted by Fang et al. revealed that a negative correlation was present between non-alcoholic fatty liver disease (NAFLD) and serum MaR1 levels [15]. They also found that the NAFLD patients had significantly higher levels of ALT, AST, GGT, ALP, urea, creatinine, and fasting blood glucose. Additionally, they highlighted the potential of MaR1 to predict and prevent NAFLD. Based on this information, we focused on the possibility that low serum levels of MaR1 could be a marker for early detection of HCC. The results of our study support our theory by showing that low MaR1 levels are associated with an increased risk of HCC.

When other biochemical parameters in the present study were examined, we found that AST, ALT, ALP, and GGT (indicators of hepatobiliary damage), CRP and leukocyte (indicators of inflammation), total bilirubin (as an indicator of biosynthetic capacity of the liver) and AFP levels were found to be significantly higher, whereas albumin levels were significantly lower in HCC patients compared to the cirrhotic and healthy groups. The association between increased liver enzymes (AST, ALT, ALP, and GGT) and HCC has been demonstrated in previous studies showing correlations with tumor aggressiveness (stage, mass, etc.) [25]. Ruhl and Everhar showed that elevated ALT and GGT levels increased the risk of liver disease-related death, but they did not find any relationship with enzyme levels and the severity of the liver cancer [26]. Hashimoto et al. revealed that preoperative serum CRP level was a significant indicator of severity and poor prognosis in HCC [27]. HCC is known to be an AFP-producing tumor, and its levels have been correlated with the tumor size and stage. Clinicians usually use serum AFP levels for the prediction and follow-up of HCC. However, AFP levels may not be consistent in every patient as they are known to be affected by many factors [28]. The sensitivity and specificity values of serum AFP level in HCC diagnosis were found to range from 39% - 65% and 76% - 94%, respectively, in previous studies [29]. We sought to determine whether any of these parameters had the potential to be used as a tumor marker in HCC or cirrhosis. In the present study, both MaR1 and AFP levels were significantly elevated in the HCC group compared to the other groups, and the independent diagnostic value of MaR1 was found to be higher than of AFP. Additionally, MaR1 was found to be a parameter that was independently associated with the presence of cirrhosis (vs. controls) and HCC (vs. controls and cirrhotic patients), suggesting that MaR1 levels are associated with cirrhosis and progression into HCC.

Our study has some limitations. The most important one is the limited number of participants, especially with respect to regression analyses. Since our study was conducted in a single center and had to be completed in a short time, the sample size remained low. Similarly, homogeneity, in terms of age and gender, could not be achieved between the study groups. Another notable limitation was that serum MaR1 levels were evaluated only once, preventing the assessment of whether the elevation in MaR1 levels was consistent. Future studies could confirm our findings and show the reliability of MaR1 levels in identifying HCC. In this study, we found that serum MaR1 levels could predict HCC in cirrhotic patients and could enable differentiation from controls and cirrhotic patients, but it is still unclear whether MaR1 levels were directly associated with progression into HCC or whether they were associated with worse cirrhotic effects in the presence of HCC.

CONCLUSION

This study demonstrated significantly lower MaR1 levels in patients with HCC compared to those with cirrhosis and lower levels in cirrhotic subjects compared to controls. Both AFP and MaR1 levels were revealed to have potential to distinguish HCC patients from healthy individuals and from patients with cirrhosis. However, the independent diagnostic value of MaR1 was found to be higher than AFP. Although this is the first study to reveal the relationship of MaR1 with HCC developing in the background of cirrhosis, our results are promising in terms of demonstrating the diagnostic value of MaR1 in this disease. Further studies with a larger sample size

and that conduct longitudinal analyses are needed to support this theory.

Declaration of Interest:

All authors meet the ICMJE authorship criteria, and all authors declare that there are no conflicts of interest regarding the publication of this article.

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