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The relationship between hepatocellular carcinoma and resolvin D1

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ABSTRACT

Aims: Liver cancer is the second most common cause of cancer death, and hepatocellular carcinoma (HCC) is the most common hepatic primary tumor. Hepatocellular carcinoma develops based on inflammation in the cirrhotic liver. The aim of our study was to determine the relationship between the decrease in Resolvin D1, the lipid mediator involved in the resolution, and hepatocarcinogenesis.

Methods: Thirty patients with HCC, thirty patients with cirrhosis, and thirty healthy subjects followed in our clinic between March 2018 and June 2019 were included in the study. Routine laboratory test results of the patients were recorded from the institutional database. Resolvin D1 and other parameters of the study groups were compared.

Results: The Resolvin D1 levels were found to be significantly different from each other group, with the ranking as follows: the HCC group (1.71±1.46 ng/ml) <the cirrhotic group (3.63±2.92 ng/ml) <the healthy control group (6.24±3.18 ng/ml) ($p<0.001$). Moreover, Resolvin D1 levels were negatively correlated with α-fetoprotein (AFP) level and tumor stage ($p<0.001$).

Conclusion: Reduced lipid mediators that aid in the resolution process cause an increase in pro-inflammatory cytokines involved in the development of hepatocellular carcinoma. A decrease in Resolvin D1 may serve as a biomarker contributing to the diagnosis of progression to HCC in cirrhotic patients by triggering chronic inflammation and hepatocarcinogenesis.

Keywords: Hepatocellular carcinoma, cirrhosis, pro-inflammatory cytokines, AFP, Resolvin D1

INTRODUCTION

Liver cancer is the fifth most common cancer globally and second in cancer-related deaths. Hepatocellular carcinoma (HCC) accounts for about 90% of liver cancers. Most patients are diagnosed at an advanced stage, resulting in limited treatment options and lower chances of successful treatment. Five-year survival is about 30-50% in patients with HCC.[1]

Cirrhosis is present in 90% of patients diagnosed with hepatocellular carcinoma.[2] The most common causes of cirrhosis are viral hepatitis and alcohol.[3] It is recommended that patients in the risk group should be screened regularly by α-fetoprotein (AFP) and ultrasonography (USG) in order to make an early diagnosis of HCC.[4] AFP is a biomarker released from cancer stem cells and is used in early diagnosis.[5]

In the cirrhotic liver, metabolic and oxidative damage due to inflammation, necrosis, and recurrent compensatory regeneration occur through pro-inflammatory cytokines. As a result, accumulated point mutations and genetic errors cause suppression of tumor suppressor genes and activation of proto-oncogenes.[3]

Special lipid mediators are involved in the resolution pathways, which represents an inflammatory response's ideal outcome. Disorders or deficiencies in the pathways associated with these lipid mediators are involved in the pathogenesis of chronic inflammatory diseases and tumors that develop due to prolonged inflammation.[6]

The lipid mediator responsible for resolution, Resolvin D1, is synthesized from doxhexanoic acid via lipoxygenase or aspirin-acetylated COX-2. Resolvin D1, through the activation of ALX/FPR2 and GPR32 receptors, lowers endothelial-neutrophil interaction, actin polymerization induced by LTB4, and the expression of CD11b, which is responsible for adhesion. Thus, it prevents the transendothelial migration of PMNL. Resolvin D1 increases the phagocytosis (efferocytosis) of apoptotic leukocytes, bacteria, and yeast particles in monocytes/mature macrophages.[7]

Resolvin D1 reduces IL-8-induced neutrophil chemotaxis. It stimulates antibody-secreting B-cell differentiation. It also reduces pro-inflammatory cytokines released from endothelial cells.[8]

Resolvin D1 also regulates the polarization of macrophages at the site of inflammation, allowing the macrophages in the M1 (pro-inflammation) pathway to convert to the M2 (anti-inflammation) pathway.[9] Thus, Resolvin D1 is effective in both ameliorating inflammation (reduces PMNL infiltration) and resolution (increases efferocytosis). It reduces necroinflammatory liver damage by reducing DNA damage and oxidative radicals in hepatocytes. A decrease in Resolvin D1 triggers both chronic inflammation and the formation of hepatocarcinogenesis via pro-inflammatory cytokines.[7]

In this study, we aimed to determine the role of Resolvin D1 in the pathogenesis of hepatocellular carcinoma and compare its levels along with AFP in cirrhotic patients with hepatocellular carcinoma, and patients with cirrhosis only and to those of healthy individuals.

METHODS

Thirty patients with hepatocellular carcinoma, thirty patients with liver cirrhosis, and thirty subjects without known health problems who were followed in the Gastroenterology Clinic of Kırıkkale University Medical Faculty Hospital were included in the study between patients and healthy individuals who accepted and signed the informed consent form participated in the study. The study was approved by the Clinical Researches Ethics Committee of Kırıkkale University Faculty of Medicine (Date: 19/03/2019, Decision No: 06/03). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The diagnosis of HCC is based on the guidelines of the European Society for Research on Liver Diseases (EASL), imaging methods (ultrasonography, magnetic resonance imaging, computed tomography), and biochemical values (AFP and liver function tests). Patients with hepatic disease other than hepatocellular carcinoma and cirrhosis, liver metastasis, or other malignancy were excluded.

Imaging methods and clinical and laboratory findings showing portal hypertension were used to diagnose cirrhosis. Individuals with chronic inflammatory diseases such as diabetes mellitus, chronic kidney disease, and collagen tissue disease, and patients who had acute infection were excluded from the healthy control group without known liver disease and alcohol use.

Blood samples were obtained from the patients included in the study after fasting for at least 12 hours. Blood samples were separated from those taken for routine tests, taken into two cc tubes, and stored in a -80°C freezer. Serum AFP levels were determined by chemoluminescence method using a cobas® e601 device and original Roche diagnostic kits. Resolvin D1 levels were assayed using the original ELISA kit (Human RvD1 ELISA kit, SUNRED). Resolvin D1 was measured quantitatively via colorimetric analysis using a spectrophotometer.

Statistical Analysis

Statistics software (SPSS 18 for windows, IBM Co., Chicago, Il, USA) is used for statistical analyses. Normality analysis of the study variables was conducted with Shapiro Wilk test.

Kruskall Wallis test was used for statistical analysis of nonparametric study findings, and $p<0.05$ was considered statistically significant. Mann-Whitney U test and Bonferroni Correction test were used in paired group comparisons, and $p<0.017$ was considered statistically significant. Non-parametric variables were expressed as medians (min-max).

The parametric study variables were analyzed using a One Way Analysis of Variance (ANOVA) test, with a significance level of $p<0.05$. Tukey Multiple Comparisons test was used in paired group comparisons, and $p<0.05$ was considered significant. These variables were expressed as means and standard deviations.

In addition, Pearson's correlation test was used to determine the correlation between the parameters of the patients.

The ROC-Curve test was used to determine the predictive characteristics of the study parameters to differentiate the disease, and the sensitivity and specificity ratios of the parameters to distinguish the disease were determined by obtaining "cut-off" values. In addition, the Logistic Regression test and Likelihood Ratio test were used to determine which of these parameters might be the best parameter for differentiation of the disease. The $p<0.05$ was considered statistically significant.

RESULTS

Thirty HCC patients, thirty cirrhosis patients, and thirty healthy people were included in the study. When the demographic characteristics of the participants were examined, it was seen that the healthy group mainly consisted of female patients, and the cirrhosis and HCC groups consisted mostly of male patients. There was no significant difference between the three groups in terms of age ($p=0.544$) (Table 1).

Considering the etiology of 60 patients included in our study, of the 30 patients in the HCC group, 17 (56.7%) were HBV, 10 (33.3%) were NASH, and the remaining 3 (10.0%) were HCV. Of the 30 patients in the cirrhosis group, 16 (53.3%) were HBV, 11 (36.7%) were NASH, 2 (6.7%) were HCV, and the remaining 1 (3.3%) had possible autoimmune etiology (Table 1).

Of the 30 patients in the HCC group, 11 (36.7%) were stage I, 10 (33.3%) were stage IIIA, 5 (16.7%) were stage IIIB, and 4 (13.3%) were stage IVB. The mean tumor size was 6.1±4.8 cm (median: 5.2; min-max: 1-22.5) (Table 1).

According to the Child-Pugh classification, 18 (60.0%) of the 30 patients in the HCC group were classified as A, 9 (30.0%) as B, 3 (10.0%) as C; of the 30 patients in the cirrhosis group, 22 (73.3%) were classified as A, 6 (20.0%) as B and 2 (6.7%) as C (Table 1).

Of the 30 patients in the HCC group, 19 (63.3%) had no acid, 3 (10.0%) had perihepatic acid, and 8 (26.7%) had common acid. Of the 30 patients in the cirrhosis group, 24 (80.0%) had no acid, and 6 (20.0%) had common acid. There was no significant difference in acidity between HCC and cirrhosis groups ($p=0.152$) (Table 1).

After the analysis applied to the patient data, Resolvin D1 ($X^2=32,927$, **$p<0.001$**), and AFP ($X^2=42,763$, $p<0.001$) were statistically different between the three groups (Table 2).

Table 1. Characteristics of participants

VARIABLE	HCC (n=30)	Cirrhosis (n=30)	Control (n=30)	Test and p-value
	n (%)			
Gender				
Female	5 (16.7)	12 (40.0)	22 (73.3)	X^2=19.819*
Male	25 (83.3)	18 (60.0)	8 (26.7)	**p<0.001**
	Average ± SD (min-max)			Test and p-value
Age (year)	62.9 ± 8.6 (45-79)	60.8 ± 11.0 (34-88)	60.5 ± 7.0 (51-78)	F=0.613 p=0.544**
Etiology				-**
NASH	10 (33.3)	11 (36.7)		
HBV	17 (56.7)	16 (53.3)		
HCV	3 (10.0)	2 (6.7)		
Autoimmune	-	1 (3.3)***		
Stage		-		-
I	11 (36.7)			
IIIA	10 (33.3)			
IIIB	5 (16.7)			
IVB	4 (13.3)			
Child-Pugh				-****
A	18 (60.0)	22 (73.3)		
B	9 (30.0)	6 (20.0)		
C	3 (10.0)	2 (6.7)		
Acid				X^2=2.052
No	19 (63.3)	24 (80.0)		p=0.152*****
Perihepatic	3 (10.0)	-		
Common	8 (26.7)	6 (20.0)		

** One-way ANOVA was performed
*** Possible autoimmune etiology
**** The test could not be performed because the expected values did not meet the Chi-square test assumptions.
***** Acid variable is re-interpreted as existent and non-existent, and then Fisher's exact test is performed

Table 2. Biochemical values

Variable	HCC Average ± SD (min-max)	Cirrhosis Average ± SD (min-max)	Control Average ± SD (min-max)	Test (F/X2) **	p-value*
AFP (ng/ml)	43.59±716 (1.40-3340)	4.46±3.255 (1.48-16.02)	2.44±1.44 (0.84-6.46)	42.763	**<0.001**
Resolvin D1 (ng/ml)	1.71±1.46 (0.28-6.05)	3.63±2.92 (0.56-11.90)	6.24±3.8 (2.35-13.45)	32.927	**<0.001**

* One Way Analysis of Variance, (ANOVA) test, Kruskal Wallis test, p <0.05
** F value

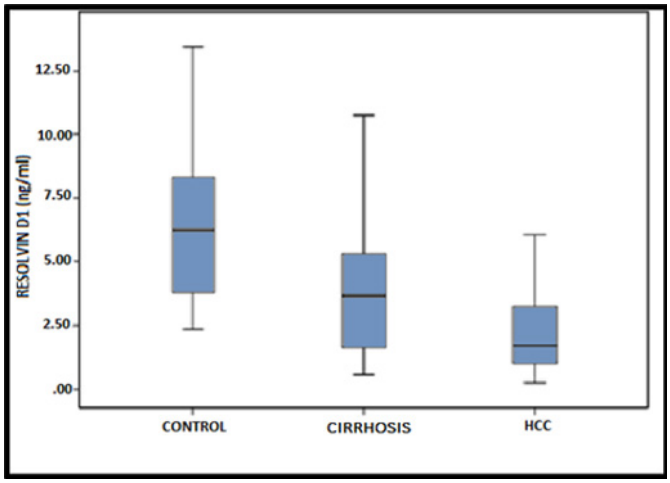

Figure 1. Distribution of Resolvin D1 levels by groups

Resolvin D1 levels were significantly different between the control and cirrhosis group (Z=-3.046, **p=0.002**), control and HCC group (Z=-5.611, **p<0.001**), and cirrhosis and HCC group (Z=-2.898, **p=0.004**). With these findings, Resolvin D1 levels were highest in the control group and lowest in the HCC group (Figure 1).

AFP levels differed between control and cirrhosis groups (Z=-3.534, **p<0.001**), control and HCC groups (Z=-5.604, **p<0.001**), and cirrhosis and HCC groups (Z=-4.716, **p<0.001**). The AFP levels were found to be the lowest in the control group and the highest in the HCC (Figure 2).

There was a significant difference between the three groups in terms of gender, resolvin D1 levels and AFP values (Table 3).

At the end of the correlation analysis, a negative correlation was found between Resolvin D1 and AFP (r=-0.429, p<0.001) and Resolvin D1 and tumor stage (r=-0.509, p<0.001). It is thought that Resolvin D1 level could be found as low while AFP level or tumor stage increases.

On the other hand, there was a positive correlation between AFP and acid form (r=0.236, **p=0.025**), AFP, and tumor stage (r=0.625, **p<0.001**). It is thought that if the AFP level is measured as high, there is the possibility of widespread acidity in the patients, and the current stage of the tumor may be increased if the patient has a tumor.

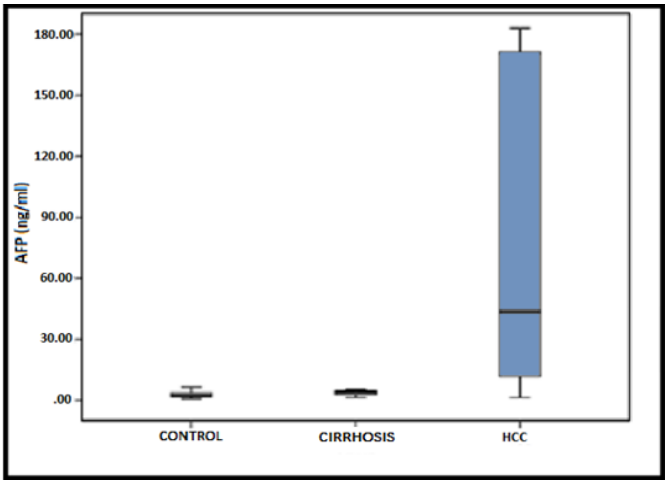

Figure 2. Distribution of alpha-fetoprotein levels by groups

Table 3. Evaluation of differences between groups

Variable	Group	Mean Difference / Z	p
Gender (F=1 M=2)	Control / Cirrhosis	-2.583	**0.010**
	Control / HCC	-4.375	**<0.001**
	Cirrhosis / HCC	-1.989	**0.047**
Resolvin D1	Control / Cirrhosis	-3.046	**0.002**
	Control / HCC	-5.611	**<0.001**
	Cirrhosis / HCC	-2.898	**0.004**
AFP	Control / Cirrhosis	-3.534	**<0.001**
	Control / HCC	-5.604	**<0.001**
	Cirrhosis / HCC	-4.716	**<0.001**

(*) mean difference value, Tukey Multiple Comparisons test, Mann-Whitney U test, p <0.05

At the end of the ROC-Curve test, it is predicted that when Resolvin D1 value<2.64 (area =0.271, **p=0.002**, sensitivity 67%, specificity 93%) and AFP value>2.91 (area=0.766, **p<0.001**, sensitivity 80%, specificity 70%), these parameters could differentiate cirrhosis patients from the control group (Table 4).

Table 4. Specificity and sensitivity of the parameters of the groups

Group	Variable	Area	p	Cut-off	Sensitivity	Specificity
Control-Cirrhosis	RESOLVİN D1	0.271	**0.002**	<2.64	%67	%93
	AFP	0.766	**<0.001**	>2.91	%80	%70
Control-HCC	RESOLVİN D1	0.078	**<0.001**	<2.46	%74	%96
	AFP	0.921	**<0.001**	>4.31	%83	%83
Cirrhosis-HCC	RESOLVİN D1	0.282	**0.004**	< 3.41	%84	%60
	AFP	0.854	**<0.001**	> 5.63	%80	%84

ROC curve test, p<0.05

At the end of the ROC-Curve test, it is predicted that when Resolvin D1 value<2.46 (area=0.078, **p<0.001**, sensitivity 74%, specificity 96%) and AFP value>4.31 (area=0.921, **p<0.001**, sensitivity 83%, specificity 83%), these parameters could differentiate HCC patients from healthy patients (Table 4).

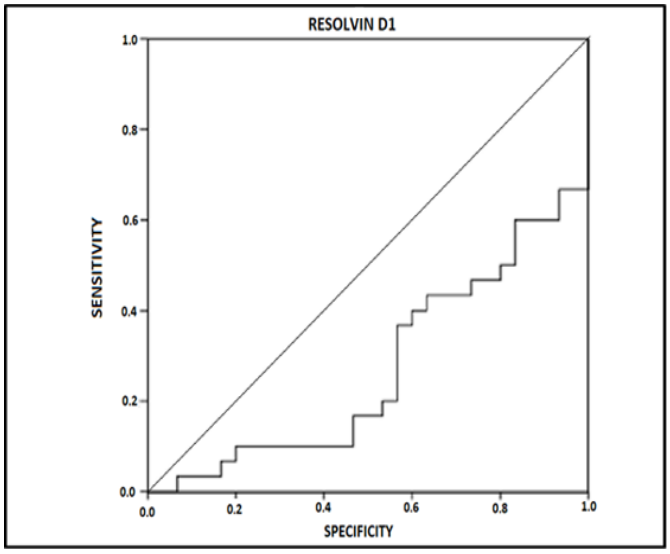

Figure 3. ROC-Curve graph of Resolvin D1 variable which can differentiate cirrhosis patients from control group

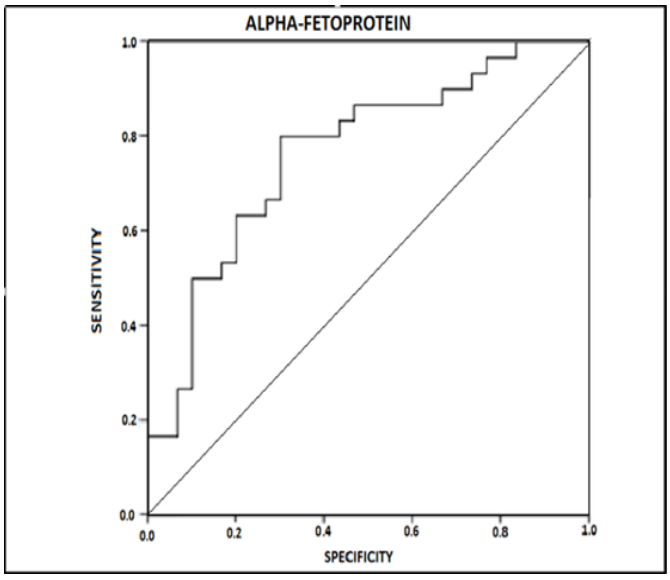

Figure 4. ROC-Curve graph of alpha-fetoprotein variable that can differentiate cirrhosis patients from control group

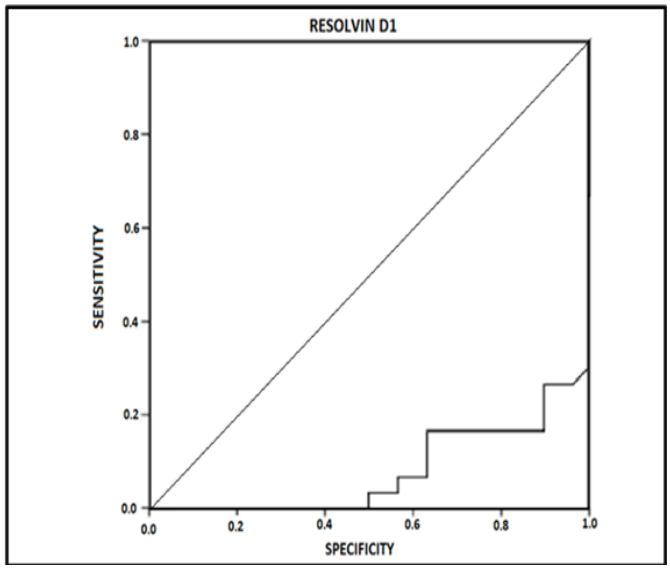

Figure 5. ROC-Curve graph of Resolvin D1 variable that can differentiate HCC patients from healthy subjects

At the end of the ROC-Curve test, it is predicted that when resolvin D1 value<3.41 (area=0.282, p=0.004, sensitivity 84%, specificity 60%) and AFP value>5.63 (area=0.854, p<0.001, sensitivity 80%, specificity 84%), these parameters could differentiate HCC patients from cirrhosis patients (Table 4).

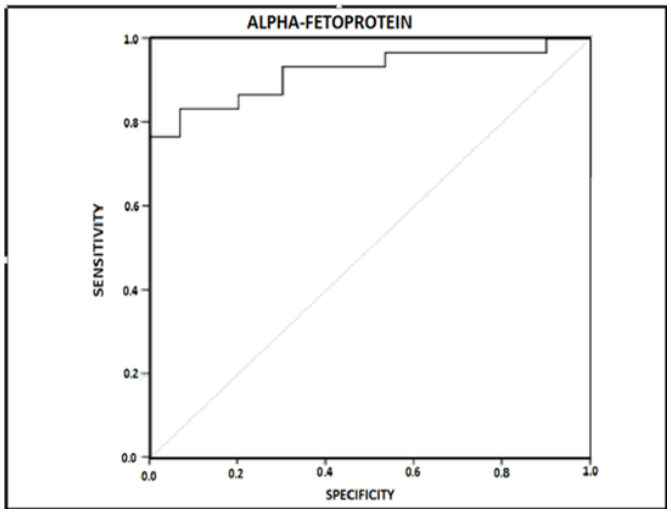

Figure 6. ROC-Curve graph of alpha-fetoprotein variable that can distinguish HCC patients from cirrhosis patients

DISCUSSION

Our study revealed significant statistical differences in the level of Resolvin D1 between the HCC and control groups, cirrhosis and control groups, and the HCC and cirrhosis groups. Specifically, Resolvin D1 levels were lower in the HCC group than the cirrhosis group and lower in the cirrhosis group than the control group. Furthermore, a negative correlation was observed between the degree of inflammation and the level of Resolvin D1. Our findings indicate a gradual decline in Resolvin D1 levels during the progression of inflammation and the development of carcinogenesis.

In our study, all patients diagnosed with hepatocellular carcinoma exhibited cirrhotic liver, and the leading etiologies of both conditions were chronic HBV infection, NASH, and chronic HCV infection. Correspondingly, Akinyemiju and colleagues 10 reported that HBV infection accounted for approximately 54% of HCC cases, while HCV infection and other causes accounted for 31% and 15%, respectively. Our study also revealed chronic HBV infection as the most common cause of HCC, and this was consistent in both Africa and East Asia. However, in Western countries, HCV infection is the predominant cause.[10]

It is known that pro-inflammatory cytokines are increased, and mediators related to resolution decrease in chronic inflammatory diseases and tumor microenvironments.[11] Navarini et al. found that in 30 patients with systemic lupus erythematosus (SLE), the Resolvin D1 level is lower than in the healthy group.[12] Fedirko et al.[13] showed that there was no association with Resolvin D1 in patients with colon adenoma in their first human study of 200 patients. Conversely, Morshedzadeh and colleagues 14 reported lower levels of Resolvin D1 in 60 patients with polycystic ovary syndrome compared to healthy individuals, with a corresponding development of subclinical inflammation. Zhuang and colleagues 15 discovered that inflammatory cytokines were elevated and Resolvin D1 levels were reduced in 50 individuals with colon cancer. Moreover, they observed a decrease in Resolvin D1 levels in correlation with the advancement of the cancer stage. Similarly, in patients with metastatic liver cancer, Resolvin D1 levels were found to be low in the early period after resection and raised in the late period.[16]

There are many experimental studies on Resolvin D1. Kuang et al.[17] showed in a study with mice that Resolvin D1 reduces inflammatory cytokines (TNF-α, IFN-γ, IL-2, IL-1β, and IL-6) and NF-κB signaling in concanavalin-induced liver cancer. Sulciner et al.[18] reported that cell debris caused by cytotoxic chemotherapy in lung cancer is increased clearance with Resolvin D1 and may be used in addition to cytotoxic chemotherapy.

Kang et al.[19] found that Resolvin D1 reduces pro-inflammatory cytokines in ischemic liver injury and changes macrophage polarization from the M1 pathway to the M2 pathway. Lee et al.[20] showed that Resolvin D1 reduces metastasis and inhibits TGF-β1 via its ALX/FPR2 and GPR32 receptors in lung cancer. Deyama et al.[21] found anti-depressant effects of Resolvin D1 in lipopolysaccharide-induced depression models. Collectively considering our study alongside other experimental studies, we can gain a more comprehensive understanding of the role and significance of Resolvin D1 in the pathogenesis of hepatocellular carcinoma.

The cirrhotic process represents a significant predisposing factor for developing hepatocellular carcinoma, highlighting the need for close monitoring of cirrhotic patients to facilitate early detection of HCC. Previous studies have demonstrated a negative correlation between alpha-fetoprotein (AFP) levels and the prognosis of HCC 22,23, whereas Yan and colleagues 24 observed a positive correlation between AFP levels and the development and tumor stage of HCC in a cohort of 24 HCC and 62 HBV-related liver cirrhosis patients. AFP protein is a valuable diagnostic tool for identifying hepatocellular carcinoma in cirrhotic and healthy populations. Our study results suggest that AFP measurements can effectively distinguish between the HCC and cirrhosis group, HCC and control group, and cirrhosis and control groups (p<0.001). Furthermore, we observed a negative correlation between tumor stage and AFP levels with Resolvin D1, indicating that decreased Resolvin D1 could serve as a critical indicator for both the diagnosis and progression of hepatocellular carcinoma.

Our study found no significant difference in the Child-Pugh scores between cirrhotic patients and those with HCC. However, we did observe lower levels of Resolvin D1 in patients with HCC compared to those with cirrhosis, providing further evidence for the involvement of Resolvin D1 in the development of hepatocellular carcinoma. Regarding diagnostic accuracy, our study found that AFP protein had a sensitivity and specificity of 83% and 83%, respectively, in distinguishing the HCC group from the control group. Meanwhile, Resolvin D1 had a sensitivity and specificity of 74% and 96%, respectively. The sensitivity and specificity of AFP protein were found to be 80-84% and 84-60%, respectively, in differentiating the cirrhosis and HCC groups. In contrast, the sensitivity and specificity of Resolvin D1 were 84-60%, respectively. Although Resolvin D1 was the best parameter in differentiating the healthy and HCC groups in our study, AFP was more effective in differentiating the cirrhosis and HCC groups, as well as the healthy and cirrhosis groups.

Study limitations: Our study is the first clinical study to reveal the relationship between resolution pathways and

hepatocellular carcinoma. However, further clinical trials with larger patient populations are required to determine the exact role of Resolvin D1 in the pathogenesis of HCC. The limited number of patients is one of the limitations of our study. The sample size in our study was relatively small, which may limit the generalizability of our findings. A larger sample size would have allowed for a more robust statistical analysis and increased the power to detect significant associations between Resolvin D1 levels and HCC. Furthermore, our study only measured Resolvin D1 levels at a single time point. This cross-sectional design does not provide information on the temporal relationship between Resolvin D1 levels and HCC development or progression. Longitudinal studies with repeated measurements of Resolvin D1 would provide more comprehensive insights into the association between Resolvin D1 and HCC. Moreover, our study did not assess other potential confounding factors that may influence the relationship between Resolvin D1 and HCC, such as genetic predisposition, lifestyle factors, or comorbidities. The lack of adjustment for these variables may have limited our ability to fully evaluate the true association between Resolvin D1 and HCC. Lastly, the measurement of Resolvin D1 itself may have certain limitations. The assays used to quantify Resolvin D1 levels may have inherent variability and measurement error. Additionally, Resolvin D1 metabolism and clearance rates may vary among individuals, which may have influenced the observed levels in our study population. Overall, while our study provides preliminary insights into the relationship between Resolvin D1 levels and HCC, these limitations should be recognized and taken into consideration when interpreting the results. Future studies with larger sample sizes and comprehensive adjustment for potential confounding factors are needed to further elucidate this relationship.

CONCLUSION

Our study found that Resolvin D1 is the most influential parameter for distinguishing individuals with HCC from healthy individuals. We also found a negative correlation between Resolvin D1 levels and both AFP level and tumor stage. These findings suggest that Resolvin D1 could be a valuable tool for predicting the development of HCC in patients with cirrhosis. However, further long-term prospective studies involving larger patient populations are needed to fully understand the diagnostic and prognostic potential of Resolvin D1 in clinical practice.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Clinical Researches Ethics Committee of the Kırıkkale University Faculty of Medicine (Date: 19/03/2019, Decision No: 06/03).

Informed Consent: All patients signed and free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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