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Prognostic Factors in Thyroid Papillary Microcarcinoma

Tiroid Papiller Mikrokarsinomda Prognostik Faktörler

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Abstract

Aim: Our aim in this retrospective study is to evaluate the factors that are important in the prognosis of thyroid papillary microcarcinoma.

Material and Method: This study is a retrospective study. In the study, 277 thyroid papillary microcarcinoma nodules belonging to 178 patients, diagnosed in Kütahya University of Health Sciences Hospital, between 2010 and 2020, were included. The prognostic significance of tumor diameter, unilaterality, bilaterality, multifocality, number of tumor foci, fibrosis, distance from the capsule and Gal-3, HBME-1 and CK19 staining were investigated retrospectively by comparing with negative prognostic factors such as lymphovascular invasion, lymph node metastasis, capsular invasion and extrathyroidal spread. Moreover, the relationship between immunostains and fibrosis was examined.

Results: The significant association was found between >0.5 tumor diameter and lymph node metastasis. Unilaterality, bilaterality, multifocality and number of tumor foci was associated with lymphovascular invasion and lymph node metastasis. Fibrosis was associated with capsular invasion and extrathyroidal spread. A correlation was found between the prevalence of Gal-3 and capsular invasion and extrathyroidal spread, and between the prevalence of CK-19 and lymph node metastasis. A positive correlation was found between fibrosis and Gal-3 and CK19, and negative correlations with HBME-1 intensity.

Conclusion: Negative prognostic markers are >0.5 tumor diameter, unilaterality, bilaterality, multifocality, number of tumor foci, fibrosis, Gal-3 and CK19 prevalence. A positive correlation was found between fibrosis and Gal-3 and CK19, and negative correlation with HBME-1 intensity.

Keywords: Thyroid papillary microcarcinoma, prognosis, Gal-3, HBME-1, CK19, fibrosis

Öz

Amaç: Bu retrospektif çalışmadaki amacımız, tiroid papiller mikrokarsinom prognozunda önemli olan faktörleri değerlendirmektir.

Gereç ve Yöntem: Bu çalışma retrospektif bir çalışmadır. Çalışmaya Kutahya Sağlık Bilimleri Üniversitesi Hastanesi'nde, 2010-2020 yılları arasında tanı konulan, 178 hastaya ait 277 tiroid papiller mikrokarsinom nodülü dahil edildi. Tümör çapı, unilateralite, bilateralite, multifokalite, tümör odak sayısı, fibrozis, kapsüle uzaklık ve Gal-3, HBME-1 ve CK19 boyanmasının prognostik önemi, lenfovasküler invazyon, lenf nodu metastazı, kapsül invazyonu ve tiroid dışı yayılım gibi negatif prognostik faktörlerle ile karşılaştırarak retrospektif olarak araştırıldı. Ayrıca Immunboyalar ile fibrozis arasındaki ilişki incelendi.

Bulgular: Tümör çapının >0,5 olması ve lenf nodu metastazı arasında anlamlı ilişki bulundu. Unilateralite, bilateralite, multifokalite ve tümör odak sayısı, lenfovasküler invazyon ve lenf nodu metastazı ile ilişkiliydi. Fibrozis, kapsül invazyonu ve ekstratiroidal yayılım ile ilişkiliydi. Gal-3 prevalansı ile kapsül invazyonu ve tiroid dışı yayılım arasında, CK-19 prevalansı ve lenf nodu metastazı arasında ilişki bulundu. Fibrozis ile Gal-3 ve CK19 yoğunlukları arasında pozitif, HBME-1 ile negatif korelasyon bulundu.

Sonuç: Negatif prognostik belirteçler >0,5 tümör çapı, unilateralite, bilateralite, multifokalite, tümör odak sayısı, fibrozis, Gal-3 ve CK19 prevalansıdır. Fibrozis ile Gal-3 ve CK19 yoğunlukları arasında pozitif, HBME-1 ile negatif korelasyon bulundu.

Anahtar Kelimeler: Tiroid papiller mikrokarsinom, prognoz, Gal-3, HBME-1, CK19, fibrozis

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INTRODUCTION

Although thyroid papillary microcarcinoma (TPMC) is generally known to be a tumor with a good prognosis,[1] there are publications reporting lymph node metastases (LNM),[2] distant metastasis (DM),[3,4] and even rare deaths.[1,3] Our aim was to determine the tumor diameter, unilaterality, bilaterality, multifocality, number of tumor foci (NTF), tumor fibrosis, distance from the capsule, and their relation with the occurrence of lymphovascular invasion (LVI), LNM, capsular invasion (CI), and extrathyroidal spread (ETS). Again, there are few studies in the literature investigating the prognostic effects of Gal-3, HBME-1 and CK19, and their association with fibrosis. There is no other publication in the literature that evaluates all parameters together.

MATERIAL AND METHOD

A total of 277 thyroid papillary microcarcinoma (TPMC) nodules belonging to 178 patients diagnosed in the Pathology Department of Kütahya University of Health Sciences Hospital, between 2010 and 2020 were included in this retrospective study. Hematoxylin-eosin (HE) slides of the patients diagnosed with TPMC were removed and re-examined retrospectively. Ethical approval was obtained (Date: 21.00.2021 , Decision No: 2021/14279).Tumor diameter, unilaterality, bilaterality, multifocality, NTF, tumor fibrosis, DFC, and prevalence of Gal-3, HBME-1 and CK19, were noted, and its relationship with negative prognostic factors such as LVI, LNM, CI, and ETS was investigated. The intensities of Gal-3, HBME-1 and CK19 stains were noted and the relationship between intensities and fibrosis was examined. In multifocal cases, the highest value was taken into account when giving tumor size, fibrosis percentage, the prevalence and intensity of Gal-3, HBME-1 and CK19, while the lowest value was taken in DFC. Statistical comparison was made by dividing the tumor into 3 groups as the DFC <0.2, 0.2-0.5 and >0.5 cm, and the tumor diameter was divided into 2 groups as those smaller and larger than 0.5 cm. When assessing immunostaining, the staining intensity was graded as: 0=none; 1=weak; 2=medium; 3=strong. The percentage of cells staining positively (prevalence) with Gal-3, HBME-1 and CK19 was scored as follows: 0=0%, 1=1-25%, 2=26-50%, 3: 51-75%, 4=76-100%.

Statistical Analysis

Mean, standard deviation, median, minimum and maximum values were given as descriptive statistics for continuous data and percentage values were given for discrete data. The data were analyzed by SPSS version 16.0 (SPSS Co., Chicago, IL, USA) for Windows. The categorical variables were expressed as numbers and percentages. The associations between variables were tested using the chi-square ($\chi 2$) test. The relationship between tumor fibrosis values and staining was analyzed by Spearman Correlation coefficient. $P<0.05$ was accepted as the statistical significance limit.

RESULTS

Of the cases, 138 (77.5) were female and 40 (22.5%) were male. Tumor diameters (n=277) were median 0.5 (0.1-1), tumor diameter mean±SD 0.51±0.50. Distance from the capsule is mean±SD 0.20±0.19 and median 0.2 (0-0.8). Lymphovascular invasion was observed in 5 (2.8%), CI in 15 (8.4%), ETS in 4 (2.2%), and lung metastasis in 1 (0.5%) case. Twenty-three (13%) of 178 patients also underwent lymph node dissection which 6 were metastatic. Since there was 1 case with lung metastasis, it was not included in the statistical evaluation. The number of associated TPMC nodules was 1-6, the percentage of tumor fibrosis was mean±SD 20.36±24.35, and the median was 5 (0-95). The tumor (n=277) was located in the right lobe in 151 (54.5%) cases, the left lobe in 101 (36.5%) cases, and the isthmus in 25 (9%) cases.

The associations between tumor characteristics and prognostic parameters of tumors are shown in **Table 1**.

Tumor Diameter

The significant associations was found between ≥ 0.5 tumor diameter and LNM ($\chi 2=5.425$, $P=0.02$).

Unilaterality, Bilaterality, Multifocality

The significant associations was found between unilaterality, bilaterality, multifocality and LVI and LNM ($\chi 2=9.417$, $P=0.002$, $\chi 2=6.668$, $P=0.01$; $\chi 2=4.362$, $P=0.04$, $\chi 2=13.692$, $P=0.000$; $\chi 2=4.477$, $P=0.03$, $\chi 2=6.241$, $P=0.01$, respectively).

Number of Tumor Focus (NTF)

The significant associations was found between NTF and LVI, LNM ($\chi 2=17.520$, $P=0.004$; $\chi 2=56.282$, $P=0.000$, respectively).

Fibrosis

There was a statistically significant relationship between CI, ETS and tumor fibrosis percentage ($\chi 2=35.195$, $P=0.000$; $\chi 2=14.796$, $P=0.002$). (**Figure 1**).

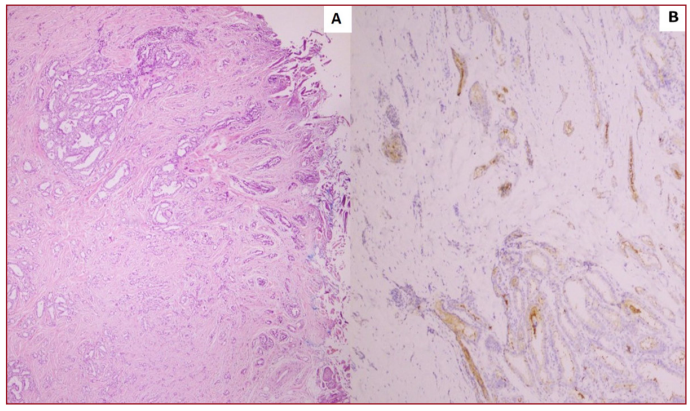

Figure 1. Capsular invasion (HEx40) B-Gal-3 positivity in tumors with intense fibrosis (X100)

Tumor-Distance From The Capsule (DFC)

There was a statistically significant relationship between CI and tumor DFC ($\chi 2=8.329$, $P=0.016$, respectively).

The Relationship between Fibrosis and Intensity of Gal-3, HBME-1 and CK19

The associations between tumor characteristics and prevalence of Gal-3, HBME-1 and CK19 are shown in **Table 2**. A relationship was found between prevalence of Gal-3 and CI and ETS (χ2=10.703, P=0.013; χ2=20.528, P=0.000) (**Figure 1**). There was no statistical significant associations prevalence of HBME-1 with tumor characteristics. There was a statistically significant relationship between prevalence of CK-19 and LNM (χ2=11.186, P=0.01).

Table 1. The associations between tumor characteristics and prognostic parameters of tumor (Each case was evaluated separately).

n=178 n (%)		Lymphovascular invasion		Lymph node metastasis		Capsular invasion		Extrathyroidal spread	
		-	+	-	+	-	+	-	+
Diameter	> 0.5	91 (95.8)	4 (4.2)	89 (93.6)	6 (6.4)	87 (91.6)	8 (8.4)	93 (97.9)	2 (2.1)
	≤ 0.5	82 (98.8)	1 (1.2)	83 (100)	0 (0)	76 (91.5)	7 (8.5)	81 (97.6)	2 (2.4)
X2 / p		1.466 / 0.226		5.425 / 0.02*		0.009 / 0.998		0.019 / 0.891	
Unilaterality -	-	136 (99.3)	1 (0.7)	135 (98.5)	2 (1.5)	128 (93.4)	9 (6.6)	135 (98.5)	2 (1.5)
	+	37 (90.2)	4 (9.8)	37 (90.2)	4 (9.8)	36 (85.7)	6 (14.3)	39 (95.1)	2 (4.9)
X2 / p		9.417 / 0.002*		6.668 / 0.01*		2.660 / 0.103		1.678 / 0.195	
Bilaterality -	-	137 (98.6)	2 (1.4)	138 (99.3)	1 (0.7)	129 (92.8)	10 (7.2)	136 (97.8)	3 (2.2)
	+	36 (92.3)	3 (7.7)	34 (87.2)	5 (12.8)	34 (87.2)	5 (12.8)	38 (97.4)	1 (2.6)
X2 / p		4.362 / 0.04*		13.692 / 0.000*		1.249 / 0.264		0.023 / 0.880	
Multifocality -	-	114 (99.1)	1 (0.9)	114 (99.1)	1 (0.9)	108 (93.9)	7 (6.1)	114 (99.1)	1 (0.9)
	+	59 (93.7)	4 (6.3)	58 (92.1)	5 (7.9)	55 (87.3)	8 (12.7)	60 (95.2)	3 (4.8)
X2 / p		4.477 / 0.03*		6.241 / 0.01*		2.306 / 0.129		2.807 / 0.094	
Number of tumor foci	1	118 (99.2)	1 (0.8)	118 (99.2)	1 (0.8)	109 (91.6)	10 (8.4)	117 (98.3)	2 (1.7)
	2	36 (97.3)	1 (2.7)	36 (97.3)	1 (2.7)	36 (97.3)	1 (2.7)	36 (97.3)	1 (2.7)
	3	11 (91.7)	1 (8.3)	12 (100)	0 (0)	10 (83.3)	2 (16.7)	12 (100)	0 (0)
	≥4	8 (80)	2 (20)	6 (66.7)	4 (33.3)	8 (80)	2 (20)	9 (90)	1 (10)
X2 / p		17.520 / 0.004*		56.282 / 0.000*		8.898 / 0.113		10.049 / 0.074	
Fibrosis	0-25%	116 (97.5)	3 (2.5)	114 (95.8)	5 (4.2)	117 (98.3)	2 (1.7)	119 (100)	0 (0)
	25-49%	31 (93.9)	2 (6.1)	32 (96.9)	1 (3.1)	29 (87.9)	4 (12.1)	32 (96.9)	1 (3.1)
	50-75%	13 (100)	0 (0)	13 (100)	0 (0)	10 (76.9)	3 (3.1)	12 (92.3)	1 (7.7)
	>75%	13 (86.7)	2 (13.3)	13 (100)	0 (0)	7 (53.8)	6 (46.2)	11 (84.6)	2 (5.3)
X2 / p		2.066 / 0.559		1.171 / 0.760		35.195 / 0.000*		14.796 / 0.002*	
Distance to the capsule	< 0.2	113 (95.7)	5 (4.3)	113 (95.7)	5 (4.3)	103 (87.3)	15 (2.7)	114 (96.6)	4 (3.4)
	0.2 - 0.5	45 (100)	0 (0)	44 (97.8)	1 (2.2)	45 (100)	0 (0)	45 (100)	0 (0)
	> 0.5	15 (100)	0 (0)	15 (100)	0 (0)	15 (100)	0 (0)	15 (100)	0 (0)
X2 / p		2.616 / 0.270		0.978 / 0.613		8.329 / 0.016*		2.081 / 0.353	

Table 2. The associations between tumor characteristics and prevalence of Gal-3, HBME-1 and CK19. (Each nodule was evaluated separately).

Prevalences			Lymphovascular invasion		Lymph node metastasis		Capsular invasion		Extrathyroidal spread	
			-	+	-	+	-	+	-	+
Gal-3	1	n (%)	65 (100)	0 (0)	63 (97)	2 (3)	62 (92.5)	5 (7.5)	65 (97)	2 (3)
	2	n (%)	7 (100)	0 (0)	7 (100)	0 (0)	7 (100)	0 (0)	7 (100)	0 (0)
	3	n (%)	7 (87.5)	1 (12.5)	7 (87.5)	1 (12.5)	5 (62.5)	3 (37.5)	6 (75)	2 (25)
	4	n (%)	94 (95.9)	4 (4.1)	95 (96.9)	3 (3.1)	89 (90.8)	9 (9.1)	96 (97.8)	2 (2.2)
X2 / p			5.414 / 0.144		2.337 / 0.505		10.703 / 0.013*		20.528 / 0.000*	
HBME-1	1	n (%)	20 100)	0 (0)	20 (100)	0 (0)	20 (95)	1 (5)	20 (100)	0 (0)
	2	n (%)	5 (100)	0 (0)	5 (100)	0 (0)	5 (100)	0 (0)	5 (100)	0 (0)
	3	n (%)	13 (100)	0 (0)	12 (92)	1 (8)	11 (84.6)	2 (5.3)	13 (100)	0 (0)
	4	n (%)	135 (96)	5 (4)	135 (96)	5 (4)	127 (0.7)	13 (9.3)	136 (97.1)	4 (2.9)
X2 / p			1.396 / 0.706		1.635 / 0.652		3.250 / 0.355		1.111 / 0.774	
CK19	1	n (%)	27 (100)	0 (0)	27 (100)	0 (0)	27 (100)	0 (0)	27 (100)	0 (0)
	2	n (%)	8 (89)	1 (11)	7 (78)	2 (22)	8 (88.8)	1 (11.2)	9 (90)	0 (0)
	3	n (%)	11 (100)	0 (0)	11 (100)	0 (0)	9 (81.8)	2 (18.2)	11 (100)	0 (0)
	4	n (%)	127 (97)	4 (3)	127 (97)	4 (3)	119 90.8)	12 (9.2)	127 (97)	4 (3)
X2 / p			3.399 / 0.334		11.186 / 0.01*		4.016 / 0.260		1.468 / 0.403	

Abbreviations: χ2: Chi-square values, Gal-3: Galectin-3, HBME-1: Human bone marrow endothelial cell marker-1, CK-19: Cytokeratin 19, , P: Probability of difference, . A P value < 0.05 was considered statistically significant.

The Relationship between Fibrosis and Gal-3, HBME-1 and CK19 (correlation)

The associations between fibrosis and intensity of Gal-3, HBME-1 and CK19 (Each nodule was evaluated separately) are shown in **Table 3** and **Figure 2**. A positive correlation was found between tumor fibrosis and Gal-3 and CK19 intensity (r=0.179 p<0.052; r=0.202 p<0.025, respectively). A negative correlation was found between tumor fibrosis and HBME-1 intensity of the cases (r=-0.155 p<0.048).

Table 3- The associations between fibrosis and immunohistochemical staining intensity (Each nodule was evaluated separately).

n=277		Fibrosis n (%)				r*	p
İntensity		0-25 %	26-50 %	51-75 %	>75 %		
Gal-3	1	174 (69)	35 (14)	16 (6)	27 (11)	0.179	0.052
	2	11 (61)	5 (28)	0 (0)	2 (11)		
	3	5 (71)	0 (0)	1 (14.5)	1 (14.5)		
HBME-1	1	22 (58)	8 (21)	2 (5)	6 (16)	-0.155	0.048
	2	121 (66)	32 (19)	10 (5)	19 (10)		
	3	46 (81)	7 (12)	2 (3.5)	2 (23.5)		
CK19	1	32 (68)	5 (11)	4 (8)	6 (13)	0.202	0.025
	2	31 (72)	2 (5)	5 (11.5)	5 (11.5)		
	3	119 (64)	38 (20)	11 (6)	19 (10)		

*Spearman's Correlation Coefficient.

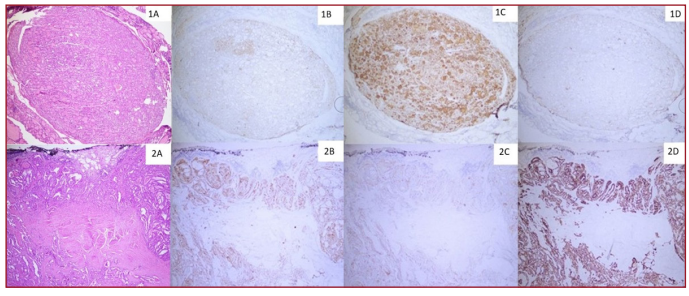

Figure 2- 1-Fibrosis negative group (X40) 2- Fibrosis positive group B-Gal-3 C-HBME-1 D-CK19 (X40).

DISCUSSION

Thyroid papillary microcarcinomas are thyroid papillary carcinomas of ≤1 cm by definition, and mortality is very low, less than 1%,[1] and mostly found incidentally.[3]

Tumor Diameter: Presence of LNM is one of the most important factors associated with local recurrence and distant metastasis.[5,6] There are publications stating that tumors larger than 0.5 mm progress more aggressively.[2,7,8] LNM ratio for tumors greater than 0.5 and less than 0.5 as follows: Goran et al. 45.71% vs. 24.34%, Lee et al. 29.1% vs. 18.2%.[2,9] This rate was also statistically significant in our study (%100 vs. %0) (p=0.02). There are also studies in the literature that do not have any difference in LNM formation.[10]

The rate of CI was higher in tumors larger than 0.5 in most studies.[2,9] This rate was 45.5 % vs. 59.8 % in Lee HS et al.'s study and 11.8% vs. 33.3% in Goran's study, and this rate was statistically significant in both studies (p<0.01).[2,9] However, in our study this rate was 8.5% vs 8.4% and do not have a statistically significant difference (χ2=0.009, P=0.998). In the group of patients with large tumors, predictor for LNM was only CI in Goran et al study.[2]

The rate of ETS in patients with TPMC varies from 2% to 53%.[10] In the study of Kim et al with 205 cases and in the study of Chow et al. with 203 case , only the rate of ETS was higher, and no difference was found in other comparisons (42.6% vs 22.2%; 29.3 % vs 4.3%).[10,11] Friguglietti et al. did not find any difference, in terms of ETS.[12] In our study, ETS was observed in 4 (2.24%) cases, and no difference was found in tumors greater than 0.5 and less than 0.5 cm group. (χ2=0.324, P=0.569)

Unilaterality, Bilaterality and Multifocality: In studies including large numbers of TPMC patients, the rate of multifocality ranges from 9.2 to 32% and that of bilaterality from 8.1 to 25.6%.[13] In our study, the multifocality rate was 35.3% and the bilaterality rate was 21.9%. Unilaterality rate was 14.7% in Goran's study, 3% in Apostol's study, and 23% in our study.[2,6] In the study of Apostol, multifocality and bilaterality were found to be associated with CI and ETS, but no significant relationship could be shown with LNM.[6] In our study, the relationship of unilaterality, bilaterality and multifocality with LVİ and LNM was statistically significant (χ2=9.417, P=0.002, χ2=6.668, P=0.01; χ2=4.362, P=0.04, χ2=13.692, P=0.000; χ2=4.477, P=0.03, χ2=6.241, P=0.01). There are publications that do not find a relationship between multifocality and LNM.[14] However, many studies have shown a relationship with LNM, as in our study.[13]

Number of tumor foci (NTF): Kim et al. reported that an increase in the NTF was strongly associated with cervical LNM, and advanced TNM stage of PTC.[11] The significant associations were found between NTF and LVI, LNM (χ2=17.520, P=0.004; χ2=56.282, P=0.000, respectively) in our study. Again, in the study of Guo et al., they suggested that LNM increased as the NTF increased in multifocal cases, and therefore they recommended more radical treatment in multifocal patients.[15]

Fibrosis: There are few publications investigating the relationship between thyroid fibrosis and prognosis. Firstly, Isarangkul et al. suggested that extensive fibrosis may be important for the diagnosis of PTC.[16] In the 511 case study of Liu et al., a relationship was found between fibrosis and LNM [17] In our study, no relationship was found between fibrosis and LNM, but a statistical difference was found between fibrosis and CI and ETS (χ2=35.195, P=0.000; χ2=14.796, P=0.002).

İmmunochemistry: Gal-3, HBME-1 and CK19, are widely used in the diagnosis of TPMC.[18] Gal-3 has been suggested to have such an effect on cancer metastasis.[19] However, a relationship was found between prevalence of Gal-3 and CI and ETS, in our study (χ2=10.703, P=0.013; χ2=20.528, P=0.000). No publication related to the prognostic significance of HBME-1 has been found in the literature. In our study, no significant relationship was found between HBME-1

with tumor characteristics. CK-19 is a poor prognostic factor whose aggressiveness is well known, mostly in liver tumors.[20] Dencic et al. found a statistically significant relationship between high CK19 expression and ETS.[21] There are studies that found a significant correlation between CK19 positivity and LNM, LVI.[22,23] In our study, a significant relationship was found between CK19 and LNM ($\chi 2=11.186$, $P=0.01$). In the Liu et al. study, IF was associated with increased Gal-3 and CK19 staining as in our study.[17] A negative correlation was found between fibrosis percentage HBME1 density ($p<0.05$). No other findings were found in the literature investigating the relationship between fibrosis and HBME-1 staining.

This study has several limitations. The first is that this is a retrospective study. The number of dissected lymph nodes is in the lower limits (13%) when compared to the literature. In the literature, this rate is 8-100%.[2] Follow-up and recurrence information were not included in the study.

CONCLUSIONS

Negative prognostic markers are >0.5 tumor diameter, unilaterality, bilaterality, multifocality, number of tumor foci, fibrosis, Gal-3 and CK19 prevalence. A positive correlation was found between fibrosis and Gal-3 and CK19, and negative correlation with HBME-1 intensity.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethical approval was obtained from Non-Interventional Clinical Research Ethics Committee of the Kutahya Health Science University Evliya Celebi Research and Training Hospital, prior to the initiation of the research work (Date: 21.00.2021 , Decision No: 2021/14279).

Informed Consent: All participants signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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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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