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The Relationship between Periostin Level and the Presence of Esophageal Varices in Patients with Decompensated Cirrhosis

Dekompanse Siroz Hastalarında Özofagus Varis Varlığı ile Periostin Düzeyleri Arasındaki İlişki

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Öz

Özofagus varisleri, dekompanse karaciğer sirozu hastalarında hastalığın şiddeti ile ilişkili olarak ortaya çıkan ve hayatı tehdit eden bir komplikasyondur. Bu çalışmada, dekompanse siroz hastalarında özofagus varis gelişimi ile serum periostin düzeyi arasında ilişki olup olmadığı incelenecektir. Dekompanse karaciğer sirozu tanısı olan ve üst GIS endoskopisi yapılan 18-70 yaş aralığındaki hastalar bu çalışmaya dâhil edildi. Hastaların serum periostin düzeyi ile özofagus varis gelişimi arasındaki ilişki incelendi. Özofagus varisi olan hastalar, varis evrelerine göre evre I, II ve III şeklinde üç gruba ayrılıp grupların periostin seviyeleri karşılaştırıldı. Hastaların 43'ü (%54.4) kadın, 36'sı (%45.6) erkekti ve yaş medyan değeri 62 (20-70) olarak hesaplandı. Hastaların 60'ında (%75.9) özofagus varisi mevcuttu (evre I; n=16, evre II; n=23, evre III; n=21). Özofagus varisi olan grubun serum periostin düzeyi, varisi olmayan gruba nazaran daha yüksekti ancak fark istatistiksel olarak anlamlı düzeyde değildi (p=0.222). Özofagus varisi olan hastalar varis evrelerine göre karşılaştırıldığında, gruplar arasında periostin seviyeleri açısından anlamlı fark yoktu (p=0.480). Korelasyon analizinde, periostin ile CHILD skoru (r=0.307, p=0.006), GPR (r=0.279, p=0.013), APRI (r=0.283, p=0.011), FIB-4 skoru (r=0.286, p=0.011) ve INR değeri (r=0.235, p=0.037) arasında pozitif korelasyon, P2/MS skoru (r=-0.275, p=0.014), trombosit (r=-0.282, p=0.012) ve albumin (r=0.356, p=0.001) arasında negatif korelasyon tespit edildi. Serum periostin düzeyi ile özofagus varisi varlığı ve varis evreleri arasında anlamlı ilişki bulunamadı. Periostin ile birçok prognostik belirteç, arasında korelasyon bulunması, periostinin siroz hastalarında potansiyel bir prognostik belirteç, olabileceğini düşündürdü.

Anahtar Kelimeler: Dekompanse Karaciğer Sirozu, Fibrozis, Özofagus Varisi, Periostin

Abstract

Esophageal varices are life-threatening complications of decompensated liver cirrhosis. Herein, it was aimed to explore the relationship between esophageal varices and serum periostin levels in decompensated cirrhosis patients. Decompensated liver cirrhosis patients (18-70 years) undergoing upper gastrointestinal (GIS) endoscopy were included in the study. The relationship between serum periostin and esophageal varices was investigated. Those with esophageal varices were divided into three groups: stages I, II, and III, and the periostin levels of the groups were compared. Forty-three (54.4%) patients were female, and the median age was 62 years (20-70 years). Sixty (75.9%) patients had esophageal varices (stage I, n=16; stage II, n=23; stage III, n=21). Although serum periostin level was higher in those with esophageal varices than those without, the difference was not statistically significant (p=0.222). Given the grades of esophageal varices, no significant difference was seen between the groups concerning periostin levels (p=0.480). In analyses, statistically significant positive correlations were found between periostin levels and Child-Pugh score (r=0.307, p=0.006), gamma-glutamyl transpeptidase to platelet ratio (GPR) (r=0.279, p=0.013), aminotransferase (AST)/platelet ratio index (APRI) (r=0.283, p=0.011), fibrosis-4 (FIB-4) score (r=0.286 p=0.011), and international normalized ratio (INR) value (r=0.235, p=0.037), and negative correlations between periostin levels and P2/MS scores (r=-0.275, p=0.014), platelet (r=-0.282, p=0.012) and albumin (r=0.356, p=0.001). There was no significant relationship between serum periostin levels and the presence and grade of esophageal varices. The correlation between periostin and other prognostic markers suggested that periostin might be a potential prognostic marker in cirrhosis patients.

Keywords: Decompensated Liver Cirrhosis, Fibrosis, Esophageal Varices, Periostin

Introduction

Liver fibrosis is a disease characterized by hepatic failure led by such factors as hepatitis B, hepatitis C, alcohol intake and autoimmunity, and the accumulation of collagen which is an extracellular matrix protein. In those having decompensated liver cirrhosis, esophageal varices are likely to develop secondary to portal hypertension because of liver fibrosis along with increased sinusoidal pressure (1).

Commonly found in such body parts as the stomach, placenta, uterus, breast tissue, aorta, lower gastrointestinal tract, and thyroid, periostin is a 90 kD extracellular matrix protein consisting of 836 amino acids and was named periostin since it was first identified in the periosteum of long bones. Various studies have shown that periostin is responsible for pathological processes such as atherosclerosis, fibrosis, metastasis, and tumorigenesis. Additionally, the chronic

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inflammation of the periostin has also been revealed to regulate the deposition of collagen by supporting the fibrosis process when secreted from fibroblasts and altering the mechanical features of the connective tissues (2).

Depending on the reasons behind liver damage, hepatic stellate cells (HSHs) or activated portal fibroblasts are the most important cells responsible for fibrosis. It has been recently demonstrated that integrins, having notable functions such as migration, proliferation, and maintenance of survival, are expressed by HSHs. Because of the way periostin and integrins interact, periostin is considered to control the progression of hepatic fibrosis by altering the activities of HSHs. The expression of periostin was found to be higher in liver biopsy tissue and HSHs in those with liver cirrhosis than in the controls (3). To our knowledge, however, no clinical study has been carried out, investigating the level of periostin in those having decompensated cirrhosis, especially those with esophageal varices.

Esophageal varices are life-threatening complications related to the severity of liver cirrhosis. Therefore, our study aimed to look at the relationship between the development of esophageal varices and serum periostin levels in those having decompensated cirrhosis.

Material and Method

Design of The Study and Patients' Selection

Seventy-nine patients diagnosed with decompensated liver cirrhosis through upper GIS endoscopy (18-70 years of age) were admitted to the departments of Gastroenterology and Internal Diseases in The Education and Research Hospital of Konya at Health Sciences University between January 2018 and 2019.

Our study was commenced after approval was obtained from the Non-Pharmaceutical and Medical Device Research Ethical Board of the Medical School of Karatay University of Konya Trade Chamber (Date: June 5, 2018, and number: 2018/015) under the World Medical Association (WMA) Declaration of Helsinki, later the October 2013 amendment of "Ethical Principles for Medical Research Involving Human Subjects". Our research was funded by Konya Training and Research Hospital of the University of Health Sciences Türkiye.

We did not include the women with pregnancy and such advanced co-morbid diseases as ulcerative colitis, asthma-chronic obstructive pulmonary disease, and malignancy, and those with non-cirrhotic portal hypertension; we also excluded the individuals not accepting to participate before and after the study.

The subjects in this cross-sectional research were enrolled voluntarily. The volunteers were comprehensively informed about the design of the study, and written consent was obtained from those accepting to take part in the study. Diagnosed with decompensated liver cirrhosis, the patients for whom endoscopy was decided made by their follow-up physician were evaluated for the study. Periostin levels were investigated with the blood samples obtained from these patients due to routine practice. The demographic, laboratory data and endoscopy findings of the participants were recorded on patients' files, and so the association of serum periostin with esophageal varices was investigated. In addition, the relationship between the prognostic models of liver cirrhosis calculated via the clinical and available laboratory parameters, and esophageal varices was also examined.

The Child-Pugh Classification

The Child-Pugh classification was created to evaluate cirrhosis risk in patients undergoing non-shunt surgery. This classification is the modified version of the 5-variable Child-Turcotte classification used for the risk assessment in patients who will undergo the portocaval shunt surgery. Five variables in the classification are serum albumin and bilirubin levels, ascites, encephalopathy, and nutrition. In the Child-Pugh classification, the status of nutrition has been modified by prothrombin time, and the scores range from five to 15. The patients with a score of five or six are considered class A (well-compensated cirrhosis), those with a score between seven and nine are considered class B (severe functional limitation), and those with a score ranging from 10 to 15 are considered class C (decompensated cirrhosis) (4).

The Model for End-Stage Liver Disease (MELD) Score

Another model used to prognose cirrhosis is the MELD score. In this scoring system, the levels of bilirubin, creatinine, and international normalized ratio (INR) are used for predicting the 3-month survival rate. The first version of this score has been created for predicting the 3-month mortality in the cases where elective transjugular portosystemic shunts are placed, and in this version, liver diseases (cholestatic, alcoholic, etc.) are also evaluated etiologically (5).

The Model for End-Stage Liver Disease-Sodium (MELDNa) Score

Kim et al. developed this model in 2008 to estimate the 90-day mortality in sufferers awaiting liver transplantation. MELDNa was suggested to predict the 90-day mortality better than the classical MELD score and is calculated by adding the serum sodium level to the score of classical MELD using the subsequent formula (6):

MELDNa = MELD – Na - [0.025 × MELD × (140 - Na)] + 140

However, MELDNa is usually calculated online, similar to the MELD score.

The Aspartate Aminotransferase/Alanine Aminotransferase Ratio (AAR)

AST-ALT ratio (AAR) is 0.8 in healthy individuals. In various studies, a ratio>1 has been shown to indicate the presence of cirrhosis (7). However, the results reported by different studies are generally inconsistent, and the clinical utility of AAR has yet to be clear in the diagnosis of cirrhosis (8).

P2/MS

The formula of P2/MS was described by Lee et al. in the research evaluating 556 sufferers with virus-associated chronic liver disease in 2009. In this research, a relationship has been shown between the P2/MS score, and the existence of esophageal varices and degree of liver fibrosis with the following formula (9):

(Thrombocyte count, 10^9/L)^2/monocyte fraction (%) x segmented neutrophil fraction (%)

The Forns Index (FI)

Such features as the patient's age, gamma-glutamyl transpeptidase (GGT), cholesterol, and thrombocyte count are used to calculate this index. In a study, FI was also investigated in individuals with hepatitis C virus (HCV) due to its similar performances to APRI, and its formula is as follows (10):

7.811-3.131× ln (thrombocyte count) + 0.781× ln (GGT) + 3.467 × ln (age) -0.014 × cholesterol

The gamma-glutamyl transpeptidase to platelet ratio (GPR)

As described by Lemoine et al. in a 2015 study investigating 135 sufferers with chronic hepatitis B undergoing liver biopsy, the model of the GPR score is calculated by the ratio of GGT to the thrombocyte count (11). In the study, the GPR score was found to be associated with the severity of liver fibrosis.

The aminotransferase (AST)/platelet ratio index (APRI)

The APRI is performed by using serum AST and thrombocyte count. To calculate the elevation of AST, the AST level is divided by the laboratory upper limit value, and the thrombocyte count is calculated by dividing the value in mm^3 by 1000 (12).

APRI = (elevation of AST/thrombocyte count) x 1000

APRI was first studied in individuals with HCV, the co-infection of HCV and human immunodeficiency virus (HIV), and those having alcoholic liver disease (12,13). In a meta-analysis evaluating a total of 40 studies, it was reported that the cut-off APRI value of 1.0 could predict cirrhosis with 76% sensitivity and 72% specificity (13).

The Neutrophil Lymphocyte Ratio (NLR)

As an inexpensive marker and an easily accessible and reproducible indicator, neutrophil-lymphocyte ratio (NLR) reflects the systemic inflammatory response. It has been shown that elevated NLR levels are linked to poor clinical results in most malignancies and cardiac diseases. While neutrophil count generally demonstrates inflammation, low lymphocyte count indicates malnutrition and inflammatory status. In the study performed by Biyik et al., an increased level of NLR was found to be related to early mortality in those with liver cirrhosis (14).

The fibrosis-4 (FIB-4) Index

In the system of FIB-4, the biochemical values of thrombocyte count, ALT and AST, and age are used in combination; FIB-4 was found to be successful in predicting progressed fibrosis in studies evaluating those having cirrhosis and non-alcoholic fatty liver disease (NAFLD) due to chronic HCV (15,16). The index is calculated as:

FIB-4 = (age x AST)/(thrombocyte count x √ALT)

In a retrospective research where 320 NAFLD sufferers were evaluated via the FIB-4 index, while a cut-off value of 0.81 was detected to be significant in predicting liver-related complications, a cut-off value of 0.67 was found significant for predicting mortality or liver transplantation (17).

The Measurement of Periostin

The sera of the patients were centrifuged and kept at -80°C until conducting the study. The serum samples of periostin were evaluated by the enzyme-linked immunosorbent assay (ELISA) method with Periostin ELISA kits (Elabscience, Houston, TX, USA). The sensitivity of periostin was found as 0.10 ng/mL, and for the serum periostin test, the intra- and inter-run CVs (CV%) were <10%.

Statistical Analyses

The SPSS statistical package for Windows, version 21.0, was utilized to perform the statistical analyses (IBM SPSS Inc., Chicago, IL, USA). The categorical variables were shown as numbers and percentages, while the numerical variables were presented as mean±standard deviation (SD) and median (min-max). The Kolmogorov-Smirnov test was used to determine if the data were normally distributed. To show if almost all parameters were not normally distributed, the Mann-Whitney U test was performed in the presence of two independent groups, and the Kruskal Wallis test was utilized in the presence of more than two independent groups in the comparison of the numerical data. The chi-square

test or Fischer's exact test was utilized in the comparison of the categorical data between the independent groups. Additionally, the Spearman test was conducted to analyze the correlation between the numerical data since the data showed no normal distribution. A p-value less than 0.05 was accepted to indicate significance.

Results

The demographic, clinical, and laboratory features of the whole study population were compared. Of 79 decompensated cirrhosis patients in the study, 43 (54.4%) were female, and the median age was found as 62 (20-70 years). Considering the etiology of the cirrhosis patients, it was seen that the distribution of the patients was as follows: 44 cryptogenic (idiopathic), 12 HBV-related, 10 HCV-related, seven autoimmune, two cardiac-related, two alcohol-related, one diagnosed with Wilson's, and one with non-alcoholic steatohepatitis. Given the endoscopy results, however, 60 (75.9%) of the patients were detected to have esophageal varices (stage I, n=16; stage II, n=23; stage III, n=21). There was also a history of ascites in 36 (45.5%) and a history of encephalopathy in 11 (14%) individuals. Patients' clinical and demographic features are presented in Table 1.

Table 1. The comparisons of demographic and clinical characteristics of the study group under the status of varices.

Parameters	Total (n=79)	Varices (+) (n=60)	Varices (-) (n=19)	*p*
Sex (F/M)	43/36	29/31	14/5	0.053
Age (years)	57.4±12.2	57.1±11.7	58.3±14.1	0.309
Ascites (+)	36 (45.5)	32 (53.3)	4 (21.1)	*0.014
Encephalopathy (+)	11 (14.0)	10 (16.7)	1 (5.3)	0.280
CKD (+)	5 (6.3)	4 (6.7)	1 (5.3)	0.653
DM (+)	30 (38)	22 (36.7)	8 (42.1)	0.670
Hypertension (+)	22 (27.8)	16 (26.7)	6 (31.6)	0.677
CAD (+)	9 (11.4)	8 (13.3)	1 (5.3)	0.308
Cerebrovascular event (+)	2 (2.5)	2 (3.3)	0 (0)	0.574
Hgb (gr/dL)	11±2.1	10.8±2.1	11.4±1.9	0.309
Hct (%)	33.9±5.4	33.7±5.5	34.7±5.1	0.492
Thrombocyte (10^3/mm^3)	123.9±91.6	118.4±88.1	141.4±102.4	0.338
WBC (10^3/mm^3)	4826.3±2243.1	4706.1±2154.6	5205.7±2527.4	0.473
Neutrophil (10^3/mm^3)	3117.9±1747.5	3080±1775.3	3237.8±1697.8	0.667
Lymphocyte (10^3/mm^3)	1079.7±531.8	1001.1±460.3	1327.8±667.3	*0.015
Monocyte (10^3/mm^3)	482.1±227.1	493.5±232.3	446.3±212	0.434
Creatinine (mg/dL)	0.86±0.32	0.88±0.30	0.82±0.37	0.100
Albumin (gr/dL)	3.1±0.6	3.1±0.5	3.1±0.6	0.878
Total bilirubin (mg/dL)	1.8±2.3	1.9±2.6	1.3±0.7	0.195
AST (IU/mL)	52.2±44.9	48.1±36.6	65.2±64.1	0.205
ALT (IU/mL)	32.1±37.1	29.5±34.2	40.1±45.6	0.085
GGT (IU/mL)	71.3±71.9	71.4±75.5	70.7±61.1	0.578
Total cholesterol (mg/dL)	146.2±59.4	149.1±64.1	137.1±41.2	0.562
INR	1.2±0.2	1.3±0.2	1.2±0.2	0.516
Sodium (mEq/mL)	137.7±3.2	137.5±2.8	138.3±4.1	0.256
Periostin (ng/mL)	4.45±2.52	4.64±2.55	3.85±2.41	0.222
Child-Pugh score	7.2±1.8	7.5±1.8	6.4±1.3	*0.022
Child class-n (%)				
A	31 (39.2)	20 (33.3)	11 (57.9)	0.062
B	38 (48.1)	30 (50)	8 (42.1)	
C	10 (12.7)	10 (16.7)	0 (0)	
MELD score	11.3±4.1	11.5±4	10.8±4.2	0.482
MELD mortality (%)	5±3.5	5.1±3.3	4.7±4.1	0.351
MELDNa score	13.4±4.2	13.7±4	12.5±5	0.126
AAR	1.8±0.7	1.9±0.8	1.7±0.7	0.147
P2/MS	266839.3±730189.4	260772.4±797477.3	285998.2±474713.6	0.318
FI	10.1±2.1	10.1±2	9.7±2.5	0.402
GPR	2.1±2.5	2.1±2.5	2±2.9	0.578
APRI	1.8±2.1	1.8±2.1	1.9±2	0.714
NLR	3.1±1.6	3.2±1.8	2.5±0.9	0.247
FIB-4 score	6.3±4.9	6.3±5	6.3±4.9	0.845

AAR: AST/ALT ratio; ALT: Alanine aminotransferase; APRI: Aminotransferase/platelet ratio index; AST: Aspartate aminotransferase; CAD: Coronary artery disease; CKD: Chronic Kidney Disease; DM: Diabetes mellitus; FI: Forns index; F/M: Female/Male; FIB-4: Fibrosis-4 score; GGT: Gamma-glutamyl transpeptidase; GPR: Gamma-glutamyl transpeptidase to platelet ratio; Hct: Hematocrit; Hgb: Hemoglobin; INR: International normalized ratio; MELD: Model for end-stage liver disease; NLR: Neutrophil lymphocyte ratio; WBC: White blood cell. Categorical variables are shown as n (%). *: Statistically significant.

When patients' laboratory findings were examined, it was found that the mean hemoglobin (Hgb) value, the median thrombocyte count, and the median lymphocyte value were 11±2.1 g/dL, 102 (24-539) $10^3/mm^3$, and 950 (290-3490) $10^3/mm^3$, respectively. However, the median periostin level of the patients was calculated as 4.25 (0.42-8.75) ng/mL, and other laboratory parameters of those in the study group have also been presented in Table 1.

Among the parameters used for prognosing liver cirrhosis patients, while the median score of Child-Pugh was calculated as 7 (5-12), the MELD and MELDNa scores were calculated as 10 (6-26) and 12 (6-28), respectively. The findings of all prognostic formulas calculated in the study are also presented in Table 1.

Given the comparisons of demographic, laboratory, and clinical features with patients' prognostic models as regards the status of varice, the participants were put into two groups: those with (+) and (-) esophageal varices. When the demographic and clinical parameters were compared, no difference was detected in both groups as regards age and gender (p=0.309 and p=0.053, respectively). Patients' rate with ascites (53.3%) was found to be significantly increased in those with varices, compared to those without (21.1%) (p=0.014). When it comes to other demographic and clinical parameters, there was no significant difference between both groups.

When the laboratory parameters of the study groups were compared, the level of serum periostin in those with esophageal varices was found to be 4.63 ng/mL (0.42-8.75) and higher than that of the group as 3.65 ng/mL (0.64-8.48) without varices, and the difference was not statistically significant (p=0.222). However, the levels of lymphocytes in esophageal varice group were determined to be significantly lower than those among the patients without esophageal varices (p=0.015). There was no significant difference was seen between both groups regarding other laboratory parameters evaluated in the study (Table 1).

In terms of prognostic factors in the study groups, the Child-Pugh score of the group with esophageal varices was found as 7 (5-12), and the outcome was significantly higher than the score found as 6 (5-9) in the group without esophageal varice (p=0.022). As regards other prognostic parameters, no difference was determined between both groups (Table 1).

Compared concerning the demographic, clinical, and laboratory characteristics via the prognostic models according to the stage of varices, esophageal varice patients were classified as stages I, II, and III. Given the comparisons of the demographic and clinical parameters of the groups, no significant difference was seen between the three stages I, II, and III in terms of the data evaluated (Table 2).

As to the comparisons of the three groups in terms of laboratory parameters, the levels of serum periostin were seen to increase as the levels progressed from stage I to stage III; however, the difference between stages I-III was observed not to be statistically significant (p=0.480). Considering periostin levels, in addition, the difference between those with stage III varice and non-varice groups was insignificant (p=0.069). A significant difference was also detected between the groups concerning Hgb levels. The post-hoc analysis revealed that this difference stemmed from the difference between stages I and II (p=0.010). Even so, no significant difference was found between the three groups related to other parameters evaluated in the study (Table 2). When the prognostic parameters of the groups were also compared, it was seen that no significant difference was seen between stages I, II, and III regarding the data evaluated (Table 2).

Correlation Analyses

In the correlation analyses carried out to investigate whether there were associations between serum periostin, age, and other numerical laboratory and prognostic parameters, it was found that there was a moderately negative correlation with albumin, a weakly negative correlation with thrombocytes, and a weakly positive and statistically significant correlation with INR. Additionally, a statistically significant weak positive correlation was also determined between the level of periostin and such prognostic parameters as the scores of Child-Pugh, GPR, APRI, and FIB-4. A statistically significant weak negative correlation was found between periostin level and P2/MS score, as well (Table 3).

Discussion

The level of periostin was found to be higher in patients with varice than in those without, albeit statistically insignificant, in the current study examining the association between the development of esophageal varice and the serum periostin level in the patients with decompensated liver cirrhosis. No differences in periostin levels were observed between the groups when the patients were compared according to the stages of esophageal varices. While the level of periostin and scores of Child-Pugh, GPR, APRI, FIB-4, and INR value were found to be positively correlated in the correlation analysis, the P2/MS score, platelet counts, and albumin values were detected to be negatively correlated.

Table 2. The comparisons of demographic and clinical characteristics of the study group under the stages of varices.

Parameters	Stage I (n=16)	Stage II (n=23)	Stage III (n=21)	*p*
Sex (F/M)	8/8	12/11	9/12	0.816
Age (years)	61.3±10.3	57.4±10.6	53.6±13.2	0.103
Ascites (+)	7 (43.8)	13 (56.5)	12 (57.1)	0.668
Encephalopathy (+)	4 (25)	1 (4.3)	5 (23.8)	0.130
CKD (+)	2 (12.5)	0 (0)	2 (9.5)	0.247
DM (+)	6 (37.5)	11 (47.8)	5 (23.8)	0.255
Hypertension (+)	5 (31.3)	6 (26.1)	5 (23.8)	0.877
CAD (+)	3 (18.8)	3(13)	2 (9.5)	0.715
Cerebrovascular event (+)	1 (6.3)	0 (0)	1 (4.8)	0.510
Hgb (gr/dl)	12.1±1.8	10.1±1.8	10.6±2.3	*0.013
Hct (%)	36.3±4.9	32.4±5	33.1±6.1	0.083
Thrombocyte (10^3/mm^3)	105.8±75.3	138.2±116.7	106.3±54.1	0.582
WBC (10^3/mm^3)	4709.3±1741.8	4584.7±2274.4	4836.6±2386.2	0.891
Neutrophil (10^3/mm^3)	2961.8±1458.6	3010.8±1924.5	3245.7±1892.7	0.818
Lymphocyte (10^3/mm^3)	1106.2±417.1	903±403.1	1028.5±543.3	0.180
Monocyte (10^3/mm^3)	557.5±245.6	480.4±259.8	459.5±187.1	0.424
Creatinine (mg/dL)	0.8±0.4	0.9±0.2	0.8±0.2	0.245
Albumin (gr/dL)	3±0.7	3.2±0.5	3.1±0.5	0.497
Total bilirubin (mg/dL)	2.7±4.8	1.5±1.1	1.8±1	0.437
AST (IU/mL)	43.3±24.4	48.4±43.7	51.2±37.2	0.583
ALT (IU/mL)	23.5±14.4	25.5±22.8	38.4±50.9	0.393
GGT (IU/mL)	47.8±37.1	74.2±84.1	86.3±85.4	0.466
Total cholesterol (mg/dL)	130.5±58.9	153±45.7	159±82.6	0.322
INR	1.2±0.1	1.2±0.2	1.2±0.2	0.522
Sodium (mEq/mL)	138.6±4.1	136.6±2.4	137.7±1.9	0.237
Periostin (ng/mL)	4.34±2.84	4.38±2.57	5.15±2.34	0.480
Child-Pugh score	7.6±2.3	7±1.2	8±2.1	0.337
Child class-n (%)				
A	6 (37.5)	8 (34.8)	6 (28.6)	*0.081
B	6 (37.5)	15 (65.2)	9 (42.9)	
C	4 (25)	0 (0)	6 (28.6)	
MELD score	12.5±4.8	10.6±3.4	11.8±3.9	0.328
MELD mortality (%)	5.7±4.1	4.2±2.1	5.4±3.7	0.313
MELDNa score	14.1±4.8	13.6±3.7	13.5±3.8	0.808
AAR	1.9±0.5	1.9±0.6	1.8±1.1	0.636
P2/MS	117643.1±184013.2	239450.6±479237.2	393175.2±1250101.8	0.434
FI	10.8±2.3	9.8±2.1	10.1±1.5	0.603
GPR	1.9±2.3	1.9±2.2	2.6±2.8	0.682
APRI	2.2±2.8	1.5±1.7	1.8±1.8	0.526
NLR	2.8±1.5	3.5±2.1	3.2±1.6	0.494
FIB-4 score	8.8±7.5	5.4±3.6	5.4±3.3	0.583

AAR: AST/ALT ratio; ALT: Alanine aminotransferase; APRI: Aminotransferase/platelet ratio index; AST: Aspartate aminotransferase; CAD: Coronary artery disease; CKD: Chronic Kidney Disease; DM: Diabetes mellitus; FI: Forns index; F/M: Female/Male; FIB-4: Fibrosis-4 score; GGT: Gamma-glutamyl transpeptidase; GPR: Gamma-glutamyl transpeptidase to platelet ratio; Hct: Hematocrit; Hgb: Hemoglobin; INR: International normalized ratio; MELD: Model for end-stage liver disease; NLR: Neutrophil lymphocyte ratio; WBC: White blood cell. Categorical variables are shown as n (%). *: Statistically significant.

Liver fibrosis is a condition marked by the accumulation of collagen, an extracellular matrix protein, and liver failure, which can be brought on by a variety of factors. Esophageal varices can arise as a secondary cause of portal hypertension in those with decompensated liver cirrhosis because of liver fibrosis and elevated sinusoidal pressure. Few studies have been conducted in the literature suggesting periostin is involved in the pathophysiology of liver fibrosis and could be a target for treatment. Additionally, periostin levels are higher in cirrhotic patients than in healthy individuals (3). To our knowledge, though, no research has been performed related to the association between cirrhosis complications, particularly esophageal varices, and serum periostin levels; so, our study is the first to look into the connection between varices and serum periostin levels.

For the first time, the impact of periostin on the progression of liver fibrosis was documented in an animal experiment conducted by Huang et al (18). The research findings indicate a significant increase in periostin expression in liver tissue in mice with both acute and chronic liver fibrosis caused by carbon tetrachloride or bile duct ligation. In periostin-deficient mice, no liver fibrosis was manifested. The levels of fibronectin, type I collagen, carbon tetrachloride, and smooth muscle actin were observed to be significantly elevated in

periostin+/+ mice, but not to change in periostin-/- mice.

The amount of collagen-stored area as well as the serum ALT and AST levels were found to be significantly lower in periostin-/- mice, compared to periostin+/+ mice following the two-week administration of carbon tetrachloride. The transforming growth factor-beta 1 (TGF-β1) markedly increased the expression of periostin in HSHs of the mice. Following the carbon tetrachloride administration, periostin-/- mice were found to have significantly lower levels of TGF-β1 and transforming growth factor-beta 2 (TGF-β) than periostin+/+ mice. Furthermore, in the identical investigation, the serum periostin, TGF-β1, and TGF-β2 levels were assessed in 32 patients with acute hepatitis, 20 patients with chronic hepatitis, and 28 healthy individuals. The results indicated that the serum periostin level was significantly higher in patients with acute or chronic hepatitis than in the controls ($p<0.001$). Additionally, a relationship was discovered between the patient groups' TGF-β1 and TGF-β2 levels and periostin levels. In the study by Huang et al., it was concluded that periostin might be a novel mediator in the development process of hepatic fibrosis (18).

Table 3. Results of the correlation analysis between periostin levels and other numerical parameters.

Parameters	rho	*p*
Age (years)	0.020	0.859
Thrombocyte	-0.282	*0.012
INR	0.235	*0.037
Albumin	-0.356	*0.001
Child-Pugh score	0.307	*0.006
MELD score	0.189	0.096
MELDNa score	0.201	0.076
AAR	0.066	0.565
P2/MS	-0.275	*0.014
GPR	0.279	*0.013
APRI	0.283	*0.011
NLR	-0.057	0.617
FIB-4 score	0.286	*0.011

AAR: Aspartate aminotransferase/alanine aminotransferase ratio; APRI: Aminotransferase/platelet ratio index; FIB-4: Fibrosis-4 score; GPR: Gamma-glutamyl transpeptidase to platelet ratio; INR: International normalized ratio; MELD: Model for end-stage liver disease; MELDNa: Model for end-stage liver disease-sodium; NLR: Neutrophil lymphocyte ratio; rho: Spearman's correlation coefficient. *: Statistically significant.

In another study examining the relationship between liver diseases and periostin, Lv et al. compared the serum periostin levels of 56 patients with hepatocellular carcinoma (HCC), 30 patients with cholelithiasis, 27 patients with cirrhosis, and 69 healthy controls. The periostin level in the HCC group was found to be significantly higher than that of the other three groups, and the increased periostin level was suggested to be an independent predictor of the prognosis and survival for HCC patients. In the study by Lv et al., although the level of serum periostin (27.3 ng/mL) was found to be higher in the cirrhosis patients than the controls (16.7 ng/mL), the data about whether the difference was statistically significant were not reported (19); such a comparison could not be performed in our study due to lack of a control group.

As the severity of cirrhosis increases, esophageal varice becomes more common in cirrhosis patients. About 9% of patients experience the development of new varices annually, and the size of these varices grows by 10-12% per annum (20,21). As a result, early detection of varices and carrying out the required interventions are directly linked to survival (22). Only 2% of cases where no varices are found at the initial endoscopy experience hemorrhages within two years, and the rate at which small varices grow into large ones has been reported as 12% in the first and 31% in the third years (23). The gold standard for diagnosing esophageal varices is endoscopy; according to the most recent guidelines, endoscopic screening programs should include patients with liver cirrhosis (24). However, because endoscopy is an invasive procedure, not all patients find it acceptable. Additionally, the procedure has several drawbacks, such as high cost-effectiveness and variations in reporting among doctors performing the procedure (1). Because of this, several non-invasive techniques have been suggested to identify the possibility of esophageal varices, particularly to minimize unnecessary endoscopic procedures.

Low thrombocyte count, enlarged spleen, elevated Child-Pugh score, and stiffness of the liver and spleen are among the most researched markers in this regard; however, none of these tests yield conclusive findings that can be substituted by endoscopy (25).

In the current study, our goal was to lower the number of unnecessary endoscopy procedures by predicting the presence of esophageal varices by measuring the serum periostin level, a marker linked to liver cirrhosis. As one of the laboratory parameters assessed in the study, the lymphocyte count was found to be lower in patients with esophageal varices than in those without; however, no statistically significant correlation was observed between the level of periostin and the presence of varices. Regarding the clinical parameters, it was discovered that varices and ascites were related. Upon reviewing the literature, we were unable to find any studies examining the association between lymphocyte count and esophageal varices. The presence of esophageal varices was found to be associated with splenomegaly, ascites, and spider angiomas, as well as with the values of thrombocyte and bilirubin in a study by Thomopoulos et al., where 184 patients with cirrhosis were investigated. In the study, Thomopoulos et al. found no association between the presence of varices and the presence of hepatic encephalopathy, serum albumin, AST, ALT, GGT, creatinine, and INR levels (26),

which is consistent with the results of our study. However, no correlation between the presence of varices and ascites was found in a different study conducted by Sarangapani et al., evaluating 106 patients with cirrhosis. The parameters that can predict the presence of esophageal varices were found to be thrombocytopenia, splenomegaly, portal vein diameter and the ratio of thrombocyte to spleen diameter (27).

We were unable to determine any correlation between prognostic scoring systems, other laboratory parameters, and the existence of esophageal varices in the current study. In general, the findings examining the issue reported by other researchers are also controversial. According to the study by Zhang et al. involving 153 cirrhosis patients, there was a correlation between esophageal varices and FIB-4 and APRI scores, but not with AAR (28).

Furthermore, a meta-analysis assessing the connection between prognostic models and esophageal varices was published in 2015 by Deng et al. In the analysis, 12 papers on the APRI score, four on the AAR score, five on the FIB-4 score, and three on the FI score were assessed. The values of area under the curve (AUC) for APRI, AAR, FIB-4, and FI were determined to be 0.67, 0.72, 0.77, and 0.75, respectively. Additionally, the values for sensitivity and specificity were found as 0.60 and 0.67 for APRI and 0.64 and 0.63 for AAR, respectively. In light of the available data, the researchers concluded that the scores APRI, AAR, FIB-4, and FI were not as effective as upper gastrointestinal endoscopy in predicting the presence of esophageal varices (29). The value of AUC was found to be 0.941 in the study by Kim et al., looking into the P2/MS score to predict the presence of varices in 318 cirrhosis patients related to hepatitis B. According to the researchers, the P2/MS scoring system is a low-cost and easy-to-use technique that may lessen the need for endoscopy in patients with HBV-related cirrhosis (30).

In our study, there was a correlation between the values of INR, thrombocyte, and albumin and the scores of Child-Pugh, GPR, APRI, FIB-4, and P2/MS, which are indicators of the severity of liver cirrhosis and associated with its prognosis. However, no relationship was found between the development and degree of esophageal varices and serum periostin levels. We propose that periostin could be a potential marker for predicting the clinical course of liver cirrhosis because of the correlation. To support such a finding, we believe that prospective studies assessing the prognosis and survival are necessary.

There are several limitations to our study. The most significant limitation is the absence of a control group and the cross-sectional design of the study. Periostin is a recently defined marker to evaluate fibrosis, and the cut-off values such as the laboratory upper limit have yet to be defined. In addition, since the prognostic models were added to the study later, some scores were found to be lower than expected according to the patient's clinical spectrum. Although the periostin level was found to be higher in patients with varicose veins, no statistical significance could be reached due to the small size of our patients, especially because of the presence of only 16 patients in the patient group without varicose veins.

Conclusion

There was no discernible relationship between the onset of esophageal varices in our study group and serum periostin levels. The existence of a correlation between periostin, and the Child-Pugh, GPR, APRI, FIB4, and P2/MS scores, and INR, platelet, and albumin values suggests that periostin may be a potential prognostic marker in cirrhosis sufferers. Further studies including larger populations will be beneficial to elucidate the entity better, which has yet to be investigated in the literature.

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Conflict of interest statement

The authors of this work have nothing to disclose.

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