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The Relationship Between Liver Fibrosis and Golgi Protein 73 in Patients with Chronic Hepatitis B

Kronik Hepatit B'li Hastalarda Karaciğer Fibrozisi ve Golgi Protein 73 Arasındaki İlişki

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ABSTRACT

Aim: This study aimed to determine the relationship between the degree of liver fibrosis and serum Golgi protein 73 (sGP73) concentration in patients with chronic hepatitis B (HBV) infection.

Materials and Methods: A total of 124 (78 HBV-positive, 40 healthy) individuals were included in the study. The participants were classified as negative healthy individuals (Group 1); HBV surface antigen-positive, HBV DNA <2000 IU/mL, chronic HBV-infected patients without liver biopsy (Group 2); and individuals with HBV DNA ≥2000 IU/mL and liver biopsy (Group 3). Group 3 was divided into subgroups as those with fibrosis lower than stage 2 (F1) and those with fibrosis of stage 2 or higher (F2). When regrouped according to the hepatic activity index (HAI), Group 1 and 2 remained the same, while Group 3 was divided into patients with an HAI below 6 (A1) and those with HAI of 6 or higher (A2).

Results: sGP73 concentrations were 11.40±7.05 ng/mL in Group 1, 16.78±6.01 ng/mL in Group 2, 43.23±10.99 ng/mL in subgroup F1, and 48.75±10.93 ng/mL in subgroup F2. These values were significantly higher in F1 and F2 compared to Groups 1 and 2 ($p<0.05$), with no statistical difference between F1 and F2. When the mean sGP73 concentrations of Group 1, Group 2, subgroup A1 (43.42±11.15 ng/mL), and subgroup A2 (46.74±11.11 ng/mL) were compared, there was no significant difference between A2 and A1 ($p>0.05$), while the differences between the other groups were statistically significant ($p<0.05$).

Conclusion: A relationship was observed between sGP73 and liver damage in patients with HBV. Although sGP73 concentration was associated with the presence of fibrosis, the relationship between sGP73 and degree of fibrosis was weakly positive and non-significant.

Keywords: GP73, hepatitis B virus, fibrosis

ÖZ

Amaç: Çalışmamızda kronik hepatit B (HBV) tanılı bireylerde karaciğer fibrozisi derecesiyle serum Golgi protein 73 (sGP73) seviyeleri arasındaki ilişkinin belirlenmesi amaçlandı.

Gereç ve Yöntem: Çalışmaya 124 (78 HBV pozitif, 40 sağlıklı) birey dahil edildi. Hastalar karaciğer biyopsisi varlığı ve biyopside fibrozis derecesine göre gruplara ayrıldı. Sağlıklı bireyler (Grup 1), HBV yüzey antijen pozitif, HBV-DNA <2000 ıu/mL, biyopsi yapılmayan kronik HBV enfeksiyonlu bireyler (Grup 2), HBV-DNA ≥2000 IU/mL olup biyopsi yapılan bireyler (Grup 3) olarak sınıflandırıldı. Grup 3 kendi içinde fibrozis evresi 2'nin altında olan bireyler (F1), fibrozis evresi 2 ve üzeri olan bireyler (F2) olarak ayrıldı. Bu gruplama hepatik aktivite indeksi (HAİ) skoruna göre tekrar yapıldığında Grup 1 ve 2 değişmezken Grup 3 HAİ derecesi 6'nın altında olan bireyler G1, HAİ derecesi 6 ve üzeri olan bireyler G2 olarak tanımlandı.

Bulgular: Grup 1 (11,40±7,05 ng/mL), Grup 2 (16,78±6,01 ng/mL), F1 (43,23±10,99 ng/mL) ve F2 (48,75±10,93 ng/mL) sGP73 düzeyleri açısından karşılaştırıldığında F2 ile F1 arasındaki fark istatistiksel açıdan anlamsız bulunurken ($p>0,05$) diğer gruplar arasındaki farklılık istatistiksel olarak

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anlamlı bulundu (p<0,05). Grup 1, Grup 2, G1 (43,42±11,15 ng/mL) ve G2 (46,74±11,11 ng/mL)'nin ortalama sGP73 düzeyleri karşılaştırıldığında G2 ile G1 arasındaki fark istatistiksel açıdan anlamsız bulunurken (p>0,05) diğer gruplar arasındaki farklılık istatistiksel olarak anlamlı bulundu (p<0,05).

Sonuç: sGP73 ile HBV pozitif hastaların karaciğer hasarı arasında ilişki vardır. Fibrozis varlığı ile sGP73 düzeyi ilişkili olmakla birlikte fibrozis derecesindeki artış ile sGP73 düzeyi arasındaki ilişki pozitif yönlü, zayıf ve istatistiksel açıdan anlamsız bir ilişkidir.

Anahtar Kelimeler: GP73, hepatit B virüsü, fibrozis

INTRODUCTION

Hepatitis is characterized by inflammation and necrosis of the liver. Hepatitis caused by hepatitis B virus (HBV) infection is a global public health issue[1]. It is generally accepted that early diagnosis of cirrhosis and elimination of its cause can halt liver damage, increase the chances of successful transplantation, and reduce mortality. Liver biopsy is the gold standard in the diagnosis of cirrhosis[2-4]. Golgi protein 73 (GP73), which was discovered by Kladney et al.[5] in 2000, is a transmembrane glycoprotein expressed by biliary epithelial cells of the liver and normally found in the cis-Golgi complex[6]. Previous studies have shown significant increases in serum GP73 (sGP73) levels with both viral and non-viral liver diseases[7]. There are also studies showing that sGP73 levels are associated with disease stage in alcoholic liver disease and chronic hepatitis[8]. We conducted the present study to determine the relationship between the degree of fibrosis and sGP73 levels in patients positive for HBV surface antigen (HBsAg).

MATERIALS AND METHOD

Our study was conducted in accordance with the principles of the Declaration of Helsinki at Sivas Cumhuriyet University Faculty of Medicine between April and October 2018. Written informed consent was obtained from all participants. Ethical approval was obtained from the Ethics Committee of Sivas Cumhuriyet University Faculty of Medicine (decision no: 2018-01/04, date: 09.01.2018). The study was supported by Cumhuriyet University Scientific Research Projects Unit.

Patient Selection

A total of 124 individuals (78 HBV-positive, 46 HBV-negative) who were over the age of 18 years and had not received any antiviral treatment were included in the study. Subjects with any viral infection other than HBV [e.g., Human Immunodeficiency virus (HIV) or hepatitis D virus were excluded.

The participants were divided into groups according to the Ishak scoring system as HBsAg-negative healthy individuals (Group 1); HBsAg-positive, HBV DNA <2000 IU/mL, chronic HBV-infected individuals without biopsy (Group 2); and HBV DNA ≥2000 IU/mL, biopsied individuals (Group 3). Group 3 was divided into subgroups as those with fibrosis lower than stage 2 (F1) and stage 2 or higher (F2). When the classification was reassessed according to the hepatic activity index (HAI), Groups 1 and 2 remained the same, while Group 3 patients were divided into those with HAI below 6 (A1) and HAI 6 or higher (A2). Figure 1A, Figure 1B shows the algorithm for the classification of the study subjects.

Variables

Age, sex, HAI, fibrosis score, alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin, direct bilirubin, albumin, platelet (PLT) count, international normalized ratio, serum HBV DNA levels, AST to PLT ratio index (APRI), fibrosis index based on 4 factors (FIB-4), and sGP73 concentrations were compared among the groups.

$$APRI = [AST \times (\text{upper limit of normal}) / PLT\ (10^9/L)] \times 100$$

$$FIB\text{-}4 = [\text{Age (years)} \times AST\ (IU/L)] / [PLT\ (10^9/L) \times \sqrt{ALT\ (IU/L)}]$$

Measurement of sGP73

Routine biochemical tests, HBV DNA, and sGP73 were analyzed from venous blood samples taken after at least 12 hours of fasting for all subjects and before the initiation of medical treatment in patients with HBV. sGP73 was measured using a SunRed ELISA kit as per the manufacturer's instructions. Briefly, a standard solution series (concentrations of 48, 24, 12, 6, and 3 ng/mL) was prepared, and 50 µL of each standard and 40 µL of each study sample were placed into the wells of ELISA plates. Each well was added 10 µL of anti-GP73 antibody, followed by 50 µL of streptavidin-horseradish peroxidase. The plate was incubated at 37 °C for 60 minutes, then washed 5 times with a washing solution. Next, 50 µL of chromogen solution A and 50 µL of chromogen solution B were added and the plates were incubated at 37 °C for 10 minutes. After adding 50 µL of stop solution, absorbance values were read at 450 nm.

Statistical Analysis

The IBM SPSS Statistics version 22.0 (IBM Corp.) program was used to analyze the data. The data were evaluated for normal distribution with the Kolmogorov-Smirnov test. Comparisons of more than two independent groups were made using ANOVA with Tukey's post-hoc test for variables showing normal distribution and using the Kruskal-Wallis test with post-hoc Mann-Whitney U test for variables not showing a normal distribution. ROC curve analysis was performed to

determine the discriminative power of sGP73. Qualitative data were tested using chi-square tests. Differences with p<0.05 were considered statistically significant.

RESULTS

There were no significant differences among the groups in terms of demographic characteristics (Table 1). ALT values were significantly higher in F2 than in all other groups and in F1 compared to Group 1 (p<0.05). The F2 subgroup also had significantly higher AST and APRI values and lower PLT count than the other groups (p<0.05). There was also a significant difference in the comparison of FIB-4, with higher values in F2 than in all other groups (p<0.05). No other significant differences were detected among the groups (Table 2).

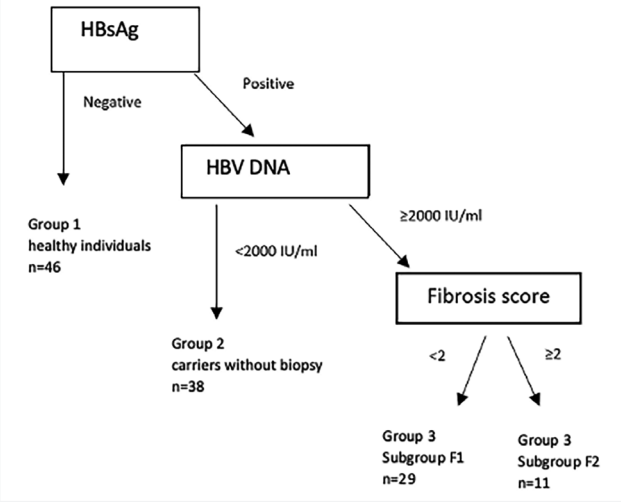

Figure 1A. The algoritm of groups according to fibrosis score
HBsAg: Hepatitis B surface antigen, HBV: Hepatitis B, HAI: Hepatic activity index

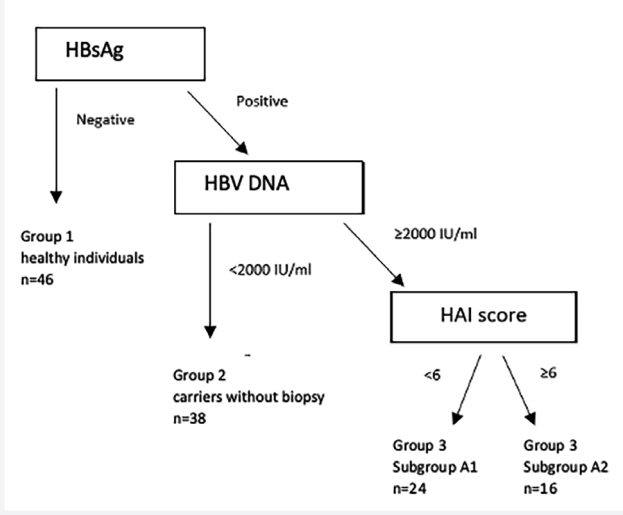

Figure 1B. The algoritm of groups according to HAI scoring
HBsAg: Hepatitis B surface antigen, HBV: Hepatitis B, HAI: Hepatic activity index

Table 1. Subject demographics

	Patients (n)	Gender (F/M)	Age (years) (mean ± SD)
	HBV DNA level		
Group 1	46	28/18	47.65±10.75
Group 2	40	18/22	46.30±13.11
Group 3	38	20/18	45.63±13.81
p-value		0.338	0.751
	Fibrosis stage		
Group 1	46	28/18	47.65±10.75
Group 2	38	17/21	45.29±12.65
F1	29	17/12	42.62±12.87
F2	11	4/7	57.18±12.23
p-value		0.287	**0.007**
	HAI grade		
Group 1	46	28/18	47.65±10.75
Group 2	38	17/21	45.29±12.65
G1	24	13/11	42.58±12.78
G2	16	8/8	52.69±14.34
p-value		0.525	0.068

F1 group: Fibrosis stage <2, F2 group: Fibrosis stage ≥2, G1 group: HAI score <6, G2 group: HAI score ≥6, SD: Standard deviation, HAI: Hepatic activity index, F: Female, M: Male, HBV: Hepatitis B

The mean sGP73 values were 11.40±7.05 ng/mL in Group 1, 16.92±5.93 ng/mL in Group 2, and 46.08±9.66 ng/mL in Group 3 (p<0.05). sGP73 concentration increased significantly between Group 1 and Group 2 and between Group 2 and Group 3 (Table 3).

When further examined by subgroup, the mean sGP73 values were 43.23±10.99 ng/mL in F1 and 48.75±10.93 ng/mL in F2. Although there was no statistical difference between F1 and F2 (p>0.05), all other pairwise comparisons indicated significant higher values in F1 and F2 than in the other groups (p<0.05). The median sGP73 values for Group 1, Group 2, F1, and F2 were 8.59 ng/mL, 16.76 ng/mL, 42.40 ng/mL, and 49.38 ng/mL, respectively. Again, F1 and F2 showed no statistical difference between themselves but had higher values than the other groups (Table 3 and Figure 2A).

When analyzed according to hepatic activity, the mean sGP73 values were 43.42±11.15 ng/mL for patients in subgroup A1 and 46.74±11.11 ng/mL for those in subgroup A2. The mean sGP73 values did not differ between A1 and A2 (p>0.05) but were significantly higher in A1 and A2 compared to the other groups (p<0.05). The median sGP73 values for Group 1, Group 2, A1 and A2 were 8.59 ng/mL, 16.76 ng/mL, 43.32 ng/mL, and 45.12 ng/mL, respectively. Although there was no significant difference between A2 and A1, there was a difference in favor of A2 between their medians (Table 3 and Figure 2B).

ROC analysis to evaluate the discriminative power of sGP73 concentration for fibrosis yielded an area under the curve (AUC) of 0.906 [95% confidence interval (CI): 0.851-0.961; p=0.001] for F1 (fibrosis stage <2). A 27.21 ng/mL cut-off value had 93.1% sensitivity and 88.4% specificity in distinguishing these patients from healthy individuals (Figure 3A). For F2 (fibrosis stage ≥2), the AUC was 0.916 (95% CI: 0.858-0.970; p=0.001) and a 37.90 ng/mL cut-off value had 90.9% sensitivity and 80.5% specificity in distinguishing from healthy individuals. (Figure 3B).

DISCUSSION

Liver fibrosis usually has an insidious onset in which most associated comorbidities and mortality manifest after cirrhosis is evident. Early diagnosis and elimination of the causes of cirrhosis may help to halt liver damage, increase successful transplantation rates, and decrease mortality[2,3]. Previous studies have suggested a relationship between sGP73 concentrations and liver disease[7,8]. In this study, we aimed to characterize the relationship between sGP73 and degree of fibrosis in HBsAg-positive patients.

Table 2. Biochemical findings relative to fibrosis stage

	Group 1	Group 2	Group 3 (F1)	Group 3 (F2)	p-value
ALT (U/L)	15.02	20.87	33.03	75.36	p<0.05*
AST (U/L)	16.63	18.26	26.03	54.64	p<0.05*
PLT (10^3/μL)	243.78	252.50	242.24	182.91	p<0.05*
APRI	0.17	0.18	0.29	0.83	p<0.05*
FIB-4	0.90	0.79	0.85	2.25	p<0.05*

FIB-4: Fibrosis index based on 4 factors, SD: Standard deviation, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, PLT: Platelet, APRI: AST to PLT ratio index, F1 group: Fibrosis stage <2, F2 group: Fibrosis stage ≥2, *p-value represents comparison between group F2 with all other groups, F1 and F2 are subgroups of Group 3 with fibrosis stage <2 and ≥2, respectively

Table 3. Mean and median sGP73 levels of all groups

		sGP73 (ng/mL) (mean ± SD)	sGP73 median (ng/mL)	p-value
HBV DNA	**Group 3**	46.08±9.66	44.89	p<0.05*
	Group 2	16.92±5.93	16.76	
	Group 1	11.40±7.05	8.59	
Fibrosis stage	**F2 group**	48.75±10.93	49.38	p<0.05*
	F1 group	43.23±10.99	42.40	
	Group 2	16.92±5.93	16.76	
	Group 1	11.40±7.05	8.59	
Grade	**G2 group**	46.74±11.11	45.12	p<0.05*
	G1 group	43.42±11.15	43.32	
	Group 2	16.92±5.93	16.76	
	Group 1	11.40±7.05	8.59	

SD: Standard deviation, HAI: Hepatic activity index, sGP73: Golgi protein 73, F1 group: Fibrosis stage <2, F2 group: Fibrosis stage ≥2, G1 group: HAI score <6, G2 group: HAI score ≥6, HBV: Hepatitis B. *P-value represents comparison between pairwise groups (except F2-F1 and G2-G1 comparisons)

Qiao et al.[9] reported a positive correlation between sGP73 concentration and HBV DNA copy number in their HBV DNA-positive group (r=0.25, p<0.01). In addition, HBV DNA-positive patients had significantly higher sGP73 concentrations than HBV DNA-negative patients (p<0.0001). Wei et al.[10] also reported significantly higher sGP73 levels in chronic HBV patients compared to the healthy population (p<0.0001). Our results are consistent with these findings. Liu et al.[11] reported a significant but very weak correlation between quantitative HBV DNA and sGP73 concentrations. In their study, sGP73 concentrations were significantly higher in patients with liver fibrosis compared to healthy individuals, hepatitis B e antigen (HBeAg)-positive chronic HBV patients, and HBeAg-negative chronic HBV patients (p<0.001 for all)[11]. Consistent with their findings, we observed a significant difference in sGP73 concentrations when the groups were stratified according to HBV DNA levels (p<0.001), and patients with fibrosis had significantly higher sGP73 concentrations compared to Groups 1 and 2 (p=0.001).

Yao et al.[12] also reported that chronic HBV patients showed higher mean sGP73 concentrations compared to the healthy control group. Similarly, we found that the HBV-positive groups

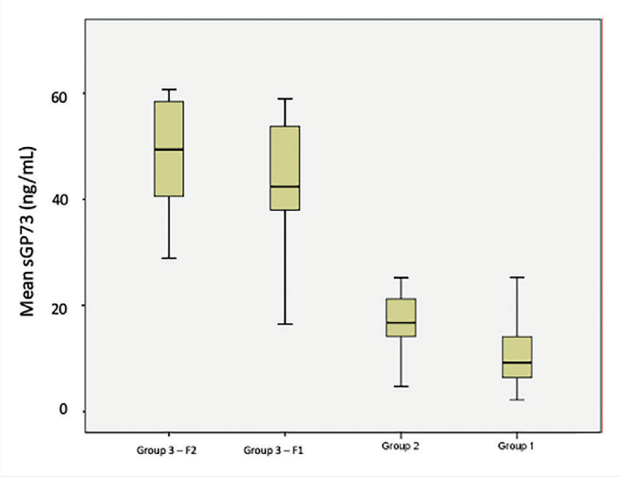

Figure 2A. Distribution of sGP73 according to fibrosis stage
sGP73: Golgi protein 73

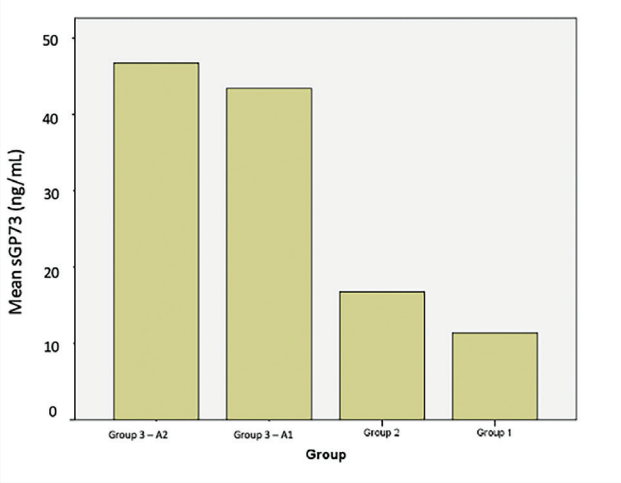

Figure 2B. Distribution of sGP73 according to HAI scoring
sGP73: Golgi protein 73, HAI: Hepatic activity index

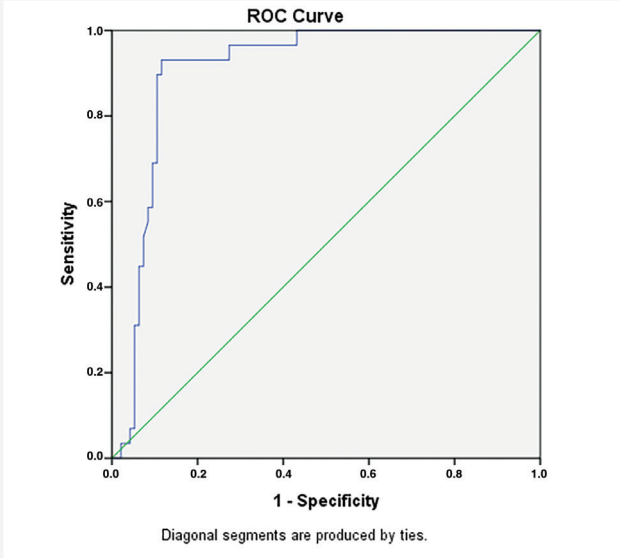

Figure 3A. ROC curve for group with fibrosis score lower than 2 (group F1)

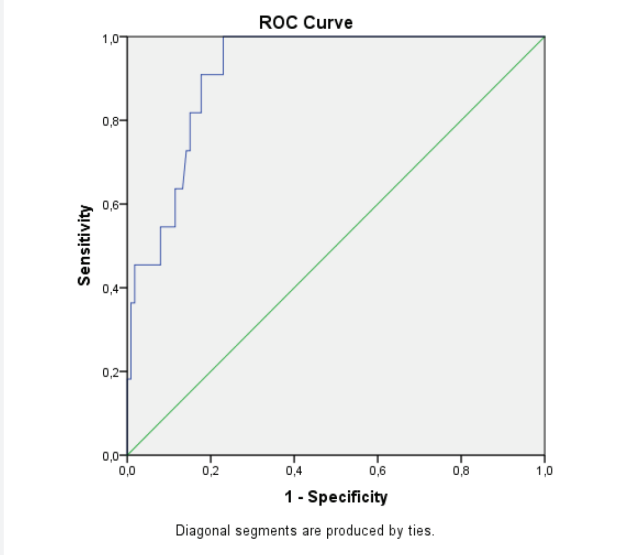

Figure 3B. ROC curve for group with fibrosis score higher than or equal to 2 (group F2)

had significantly higher sGP73 concentrations compared to controls. This result supports the view that sGP73 may be used as a biomarker of liver damage in individuals who contracted and carry HBV. Although sGP73 has also been proposed as a prognostic factor in predicting fibrosis, we observed no increase in sGP73 in relation to the degree of fibrosis, as opposed to the study by Yao et al.[12], Xu et al.[13] reported a positive correlation between sGP73 concentration and severity of liver disease in chronic HBV patients. They determined that sGP73 significantly increased with higher hepatic necroinflammatory degree and fibrosis grade. SGP73 concentrations were also positively correlated with ALT (r=0.48, p=0.001) and AST (r=0.51, p<0.001) in chronic HBV patients[13]. Our study showed that patients in the F1 and F2 subgroups, who all underwent liver biopsy, had significantly higher sGP73 concentrations compared to Groups 1 and 2 (p=0.001). This is in line with the findings of Xu et al.[13] related to chronic HBV patients and HBV carriers. However, our results did not support the relationship between sGP73 and more severe fibrosis, as no significant difference was detected between F1 and F2. Similarly, Xu et al.[13] reported no significant difference between the grade 3 and 4 fibrosis groups in their study. The increasing trend in median sGP73 towards the F2 subgroup leads us to believe that with a larger series, this difference may gain statistical significance.

Wei et al.[14] reported statistically significant differences in sGP73, AST, and PLT values between patients with and without overt fibrosis. In contrast, we did not observe a significant difference in sGP73 levels between the A1 (with overt inflammation) and A2 (without overt inflammation) subgroups. We believe that this may be due to a lower number of patients in our series, and also due to the fact that serum samples were taken from some patients during follow-up after liver biopsy. In our study, sGP73 concentrations significantly differed according to the presence of fibrosis, but not according to the degree of fibrosis (p>0.05). Although this contradicts Wei et al.[14], a comparison of median values showed that sGP73 tended to increase in F2, which concurs with their finding. Moreover, F2 had significantly higher AST and ALT values compared to the other groups, while there were no other differences. We believe that the reason for this difference is that Wei et al.[14] did not include patients with ALT value ≥2 times the upper limit of normal in their study. In our study, the mean ALT and AST levels increased from Group 1 towards F2, and the mean PLT count was found to be below normal for F2 and normal in other groups (p=0.003). Our results for AST and PLT count are similar to the findings reported by Wei et al.[14], Cao et al.[15] reported the predictive performance of sGP73 concentration to be high for overt fibrosis (AUC: 0.75, 95% CI: 0.70-0.79), severe fibrosis (AUC: 0.76, 95% CI: 0.71-0.81), and HBV-related cirrhosis (AUC: 0.75, 95% CI: 0.65-0.78). They also reported that the AUC for sGP73 in diagnosing overt fibrosis was similar to elastography and significantly higher than APRI and FIB-4, although this superiority was lower for severe fibrosis and lost for cirrhosis. Every 1 ng/mL increase in sGP73 level was associated with an odds ratio of 1.012 (95% CI: 1.005-1.019) for significant fibrosis in all patients or an odds ratio of 1.025 (95% CI: 1.014-1.036) in patients with chronic HBV infection[15]. Our study showed sGP73 to be independently associated with overt fibrosis. Cao et al.[16] also reported in another study that sGP73 was an independent predictor of fibrosis (odds ratio: 1.02, 95% CI: 1.01-1.03, per 1 ng/mL increase; p<0.001) and was not affected by HBV DNA load. In our study, when the sGP73 cut-off value was set at 37.9 ng/mL, the AUC was 0.916 for the F2 subgroup (95% CI: 0.858-0.97, p=0.001). This cut-off value had 90.9% sensitivity and 80.5% specificity in differentiating patients with stage ≥2 fibrosis from healthy controls. Although sGP73 concentrations were statistically significant in determining the presence of fibrosis, their relationship with fibrosis degree was inconclusive because of the lack of a statistical difference between the F1 and F2 subgroups. Due to the nature of the biopsy method, our insight into the status of the whole liver is inductive. Therefore, performing elastography in the groups may help clarify the relationship between the degree of fibrosis and sGP73 concentration, as in the study by Cao et al.[16] A novel study design incorporating elastography could yield more conclusive results in a less invasive fashion compared to liver biopsy.

Study Limitations

The main limitations of our study are the relatively low number of patients and the fact that for some patients, serum samples were obtained during follow-up instead of concurrently with the liver biopsy.

CONCLUSION

Our study has shown that sGP73 concentration is a viable indicator for determining the presence of inflammation and fibrosis in chronic HBV patients. These results support the hypothesis that sGP73 may be used as a valuable biomarker to predict liver damage in patients exposed to HBV. However, we were unable to corroborate the relationship between increasing sGP73 and degree of fibrosis.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Ethics Committee of Sivas Cumhuriyet University Faculty of Medicine (decision no: 2018-01/04, date: 09.01.2018).

Informed Consent: Written informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: C.İ., Concept: C.İ., A.Y., Design: C.İ., H.T., Data Collection or Processing: C.İ., H.O.D., Ş.N.Y., Analysis or Interpretation: C.İ., Literature Search: C.İ., Writing: C.İ.

Conflict of Interest: No conflict of interest was declared by the authors.

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