

Quantitative HBsAg titers in relation to disease progression and serum markers of iron metabolism among chronic hepatitis B patients

Nimet Yilmaz, Hakan Çam

ABSTRACT

Aims: To investigate quantitative hepatitis B surface antigen (HBsAg) titers in relation to disease progression and serum markers of iron metabolism in chronic hepatitis B (CHB) patients. **Methods:** A total of 99 treatment-naïve CHB patients [median (min/max) age: 39.0 (17–66) years, 61.6% were males] with HBsAg positivity for at least six months were included in this study. Data on patient demographics, quantitative HBsAg titers (IU/mL), liver enzymes, hepatitis B virus (HBV) DNA levels, fibrosis stage, necroinflammatory scores and serum iron parameters including serum Fe ($\mu\text{g/dL}$), total iron binding capacity (TIBC; $\mu\text{g/dL}$), transferrin saturation (%), and ferritin (ng/mL) were recorded and compared with respect to gender and age (median age <40 years vs. ≥ 40 years). **Results:** Serum Fe (78.2 ± 29.5 vs. 111.7 ± 36.8 $\mu\text{g/dL}$, $p = 0.001$), transferrin saturation [0.2 (0.1–0.5) vs. 0.3 (0.1–1.0) %, $p < 0.001$], and ferritin [27 (3.9–298) vs. 100 (31–994) ng/mL , $p < 0.001$] levels were significantly lower in females than in males. Quantitative HBsAg titers were correlated with age negatively in males overall ($r = -0.328$, $p < 0.001$) and positively in females >40 years of age ($r = 0.722$, $p < 0.001$). In females, quantitative HBsAg titers were positively with fibrosis stage ($r = 0.491$, $p = 0.002$), necroinflammatory grade ($r = 0.235$, $p = 0.049$), and ferritin ($r = 0.288$, $p = 0.011$) regardless of the age. In males, HBsAg titers were

positively correlated with fibrosis stage ($r = 0.501$, $p = 0.003$), necroinflammatory grade ($r = 0.471$, $p = 0.007$), and HBV DNA ($r = 0.313$, $p = 0.012$) as well as with aspartate aminotransferase (AST) ($r = 0.284$, $p = 0.021$) and alanine aminotransferase (ALT) ($r = 0.265$, $p = 0.031$) only in those >40 years of age. **Conclusion:** In conclusion, our findings revealed lower serum iron parameters and association of quantitative HBsAg with ferritin levels in females and significant association of quantitative HBsAg with hepatitis markers in females regardless of age and in males after 40 years of age. Our findings also emphasize the likelihood of the more direct role of HBV-related liver injury rather than HBV infection per se in disturbed iron metabolism among female CHB patients and stronger association of HBsAg titers with HBV DNA and liver enzymes in males after 40 years of age.

Keywords: Chronic hepatitis B, Fibrosis, Quantitative HBsAg titers, Serum iron parameters

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Nimet Yilmaz¹, Hakan Çam²

Affiliations: ¹Faculty of Medicine, Department of Internal Medicine, Division of Gastroenterology, University of Sanko, Gaziantep, Turkey; ²Private Meydan Health Institutions, Private Uncali Meydan Hospital, Division of Gastroenterology, Antalya, Turkey.

Corresponding Author: Nimet Yilmaz, Faculty of Medicine, Department of Internal Medicine, Division of Gastroenterology, University of Sanko, Gaziantep, Turkey; Email: drnimet23@hotmail.com

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INTRODUCTION

Chronic hepatitis B (CHB) infection is a common liver disorder with frequent progression to cirrhosis, and increased risk of hepatocellular carcinoma (HCC) alongside the high morbidity and mortality [1–3].

Serum hepatitis B surface antigen (HBsAg) is a reliable biomarker of active hepatitis B virus (HBV) infection [4,

5], while HBsAg loss and HBsAg seroconversion are the optimal goal of antiviral therapy [6].

Following the recent standardization by automated quantitative assays, quantitative HBsAg titers have become increasingly used in stratification of the risk of disease progression and prediction of treatment response to antiviral therapy in patients with chronic HBV infection [7–10].

Many indices of iron metabolism such as hepatic iron, serum levels of iron, ferritin, and transferrin saturation have been used as diagnostic tools in detecting iron overload as a risk factor for liver fibrosis and disease progression [11–14]. However, prevalence and clinical significance of disturbed iron metabolism in patients with HBV-related cirrhosis remain still inconclusive [3, 11, 12, 15].

This study was therefore designed to investigate the association of quantitative HBsAg titers with disease progression and serum markers of iron metabolism in CHB patients.

METHODS

Study population

A total of 99 treatment-naïve CHB patients [median age 39.0 (range, 17–66) years, 61.6% were males] with HBsAg positivity for at least six months were included in this cross-sectional study conducted in a tertiary care gastroenterology outpatient clinic. Non-HBV etiology for liver disease, past history of antiviral treatment, presence of severe systemic disease, hemochromatosis, Wilson disease, toxic or alcoholic hepatitis, malignancy, organ transplantation, anemia, or hematological disease were the exclusion criteria of the study.

Written informed consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study which was conducted in accordance with the ethical principles stated in the “Declaration of Helsinki” and approved by the institutional ethics committee. This work was supported by Gaziantep University Scientific Research Fund.

Study parameters

Data on patient demographics were recorded, while measurements for quantitative HBsAg titers (IU/mL), hepatitis B e antigen (HBeAg) status, serum AST, ALT levels, HBV DNA levels, and serum iron parameters including serum Fe ($\mu\text{g/dL}$), total iron binding capacity (TIBC, $\mu\text{g/dL}$), transferrin saturation (%), and ferritin (ng/mL) measurements were performed after enrolment in each patient. Liver biopsy findings on fibrosis stage and necroinflammatory grade were also recorded. Study parameters as well as their correlation with quantitative HBsAg titers were analyzed as stratified by age and gender. Given the impact of the menstrual blood loss of younger women on findings,

the comparison was made between men and women >40 years of age.

Serological analysis

In all the patients, HBsAg, HBeAg, and anti-HBe tests were performed using ELISA, whereas HBV-DNA tests were performed using quantitative polymerase chain reaction (Amplicor HBV Monitor test, Roche Diagnostic Systems, Inc., Branchburg, NJ) (sensitivity 60 IU/mL).

Quantitative serum HBsAg assay

HBsAg levels in the serum samples were quantified by using Architect HBsAg QT assay (Abbott Laboratories, Chicago, USA), based on a chemiluminescent microparticle immunoassay, according to the manufacturer’s protocol. The detection values of this kit range from 0.05 to 250 IU/mL, and the samples with higher than 250 IU/mL HBsAg levels require a 1:500 or greater dilution.

Liver biopsy

Each patient underwent percutaneous liver biopsies with ultrasonography-guided lateral intercostal approach, using an automatic Tru-Cut needle. Formalin-fixed paraffin-embedded sections were stained with hematoxylin and eosin and with Masson’s trichrome. The slides were reviewed by the same experienced hepatopathologist in terms of histologic activity index (HAI) using the Ishak modified HAI [16]. Modified HAI Grading was based on necroinflammatory scores (piecemeal necrosis, confluent necrosis focal necrosis, and focal inflammation) with maximum possible score of 18 [17]. Modified HAI Staging was based on architectural changes, fibrosis, and cirrhosis and scored from 0 (no fibrosis) to 6 (cirrhosis, probable, or definite) [16].

Statistical analysis

Statistical analysis was made using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). Fisher–Freeman–Halton test with Monte Carlo simulation technique was used to analyze categorical variables, while independent-samples *t*-test (Bootstrap) and Mann–Whitney *U* test (Monte Carlo) were used for analysis of numerical variables. Correlation analysis was performed via Spearman’s correlation analysis. Data were expressed as “mean \pm standard deviation (SD)” median (minimum–maximum) and percent (%) where appropriate. $p < 0.05$ was considered statistically significant.

RESULTS

Demographic and clinical characteristics of patients

Overall, median age of patients was 39 years (range, 17–66) and 61.6% were male patients. Quantitative HBsAg

titer was median (min–max) 4486 (73.81–212,000) IU/mL. Analysis of serum iron parameters revealed mean \pm SD levels for serum Fe to be 98.3 ± 37.8 μ g/dL, while median (min–max) levels for TIBC were 347.0 (129.0–495.0) μ g/dL, for transferrin saturation were 0.3 (0.1–1.0) (%), and for ferritin were 69.0 (3.9–994.0) ng/mL. HBeAg positivity was evident in 13.1% of patients (Table 1).

Serum Fe (mean \pm SD 78.2 ± 29.5 vs. 111.7 ± 36.8 μ g/dL, $p = 0.001$), transferrin saturation [median (min–max) 0.2 (0.1–0.5) vs. 0.3 (0.1–1.0) %, $p < 0.001$] and ferritin [median (min–max) 27 (3.9–298) vs. 100 (31–994) ng/mL, $p < 0.001$] levels were significantly lower in females than in males. No gender influence was noted on HBeAg status, fibrosis stage, necroinflammatory grade, quantitative HBsAg, or HBV DNA, while serum AST and ALT levels were significantly higher in males than in females (median 37 vs. 21 and 43 vs. 23 U/L, respectively, $p < 0.001$ for each) (Table 1).

Necroinflammatory grade ($p = 0.001$) and HBV DNA ($p < 0.001$) were significantly higher, whereas quantitative HBsAg ($p < 0.001$) was significantly lower

in HBeAg positive patients than in HBeAg negative patients. No significant difference was noted in serum iron parameters with respect to HBeAg status (Table 2).

Study parameters with respect to age in gender groups

When the male and females >40 years of age were compared, serum AST (median 44.0 vs. 21.5 U/L, $p = 0.001$) and ALT (median 45.0 vs. 18.5 U/L, $p < 0.001$) levels were significantly higher in males than in females, while all serum iron parameters (excluding TIBC) were significantly lower in females than in males (p ranged from 0.010 to <0.001). Fibrosis stage, necroinflammatory grade, HBV DNA, and quantitative HBsAg titers were similar in females and males >40 years of age (Table 3).

Quantitative HBsAg titers with respect to study parameters

In the overall study population, quantitative HBsAg titers were determined to be correlated negatively with

Table 1: Disease progression and serum iron markers overall and according to gender

		Total (n = 99)	Gender		p-value
			Female (n = 38)	Male (n = 61)	
Age (year), median (min–max)		39.0 (17–66)	31 (19–66)	42 (17–62)	0.120 ¹
Fibrosis stage, n (%)					
Stage 0		12 (12.1)	5 (13.2)	7 (11.5)	0.101 ²
Stage I–II		45 (45.5)	22 (57.9)	23 (37.7)	
Stage \geq III		42 (42.4)	11 (28.9)	31 (50.8)	
Necroinflammatory grade, median (min–max)		4 (1–12)	3 (1–12)	4 (1–10)	0.089 ¹
Serology markers, median (min–max)					
Serum AST (U/L)		27 (12–763)	21 (12–107)	37 (17–763)	<0.001 ¹
Serum ALT (U/L)		32 (9–801)	23 (9–207)	43 (10–801)	<0.001 ¹
HBV DNA (IU/mL), median (min–max)		34,000 (43–289,765,263)	20,500 (430–289,765,263)	66,000 (107–170,000,000)	0.459 ¹
Quantitative HBsAg (IU/mL), median (min–max)		4486 (73.8–212,000)	3922 (73.8–212,000)	5395 (212.1–194,100)	0.779 ¹
HBeAg status, n (%)					0.999 ³
	Negative	86 (86.9)	33 (86.8)	53 (86.9)	
	Positive	13 (13.1)	5 (13.2)	8 (13.2)	
Iron parameters					
Serum Fe (μ g/dL)		Mean \pm SD	78.2 ± 29.5	111.7 ± 36.8	0.001 ⁴
TIBC (μ g/dL)		Median (min–max)	364.5 (231–495)	340 (129–493)	0.066 ¹
Transferrin saturation (%)		Median (min–max)	0.2 (0.1–0.5)	0.3 (0.1–1.0)	<0.001 ¹
Ferritin (ng/mL)		Median (min–max)	27 (3.9–298)	100 (31–994)	<0.001 ¹

AST: aspartate aminotransferase; ALT: alanine aminotransferase; HBV: hepatitis B virus; SD: standard deviation; TIBC: total iron binding capacity.

¹Mann–Whitney U test (Monte Carlo); ²Fisher–Freeman–Halton test (Monte Carlo); ³Pearson Chi-Square test (Exact);

⁴Independent samples t -test (Bootstrap).

Table 2: Disease progression and serum iron markers by HBeAg status

		HBeAg status		p-value
		Negative (n = 86)	Positive (n = 13)	
Age (year), median (min–max)		40.5 (19–66)	26 (17–61)	0.069 ¹
Fibrosis stage, n (%)				
Stage 0		12 (14.0)	0 (0.0)	0.098 ²
Stage I–II		41 (47.7)	4 (30.8)	
Stage ≥III		33 (38.4)	9 (69.2)	
Necroinflammatory grade, median (min–max)		3 (1/10)	6 (3/12)	0.001¹
Serology markers, median (min–max)				
Serum AST (U/L), median (min–max)		260 (120–7630)	370 (170–2880)	0.358 ¹
Serum ALT (U/L), median (min–max)		300 (90–8010)	480 (160–5720)	0.188 ¹
HBV DNA (IU/mL), median (min–max)		200,000 (430–1,700,000,000)	1,700,000,000 (81,400–2,897,652,630)	<0.001¹
Quantitative HBsAg (IU/mL), median (min–max)		36,200 (738–2,120,000)	360,420 (22,230–1,941,000)	<0.001¹
HBeAg status, n (%)	Negative	–	–	–
	Positive	–	–	
Iron parameters				
Serum Fe (µg/dL)	Mean ± SD	982.79 ± 384.05	1032.31 ± 344.36	0.479 ³
TIBC (µg/dL)	Median (min–max)	3475 (1290–4950)	3320 (2750–4550)	0.928 ¹
Transferrin saturation (%)	Median (min–max)	3 (1/10)	3 (1–5)	0.386 ¹
Ferritin (ng/mL)	Median (min–max)	681.5 (39–9940)	700 (80–3070)	0.470 ¹

AST: aspartate aminotransferase; ALT: alanine aminotransferase; HBV: hepatitis B virus; SD: standard deviation; TIBC: total iron binding capacity.

¹Mann–Whitney *U* test (Monte Carlo); ²Fisher–Freeman–Halton test (Monte Carlo); ³Independent samples *t*-test (Bootstrap). Values in bold indicate statistical significance.

Table 3: Study parameters with respect to age in gender groups

		>40 years of age		p-value
		Females (n = 14)	Males (n = 33)	
Fibrosis stage, n (%)	Stage 0	1 (7.1)	3 (9.1)	0.074 ¹
	Stage I–II	8 (57.1)	8 (24.2)	
	Stage ≥III	5 (35.7)	22 (66.7)	
Necroinflammatory grade, median (min–max)		3 (2–9)	6 (1–10)	0.158 ²
Serum AST (U/L)	Median (min–max)	21.5 (13–86)	44 (18–763)	0.001²
Serum ALT (U/L)	Median (min–max)	18.5 (11–207)	45 (12–801)	<0.001²
HBV DNA (IU/mL)	Median (min–max)	27,500 (2360–170,000,000)	87,500 (107–170,000,000)	0.328 ²
Quantitative HBsAg (IU/mL)	Median (min–max)	3462 (369.8–45,894)	2286 (362.5–40292)	0.973 ²
Serum Fe (µg/dL)	Mean ± SD	77.2 ± 27.0	117.5 ± 36.6	0.001³
TIBC (µg/dL)	Median (min–max)	334.5 (231–432)	343.0 (129–493)	0.838 ²
Transferrin saturation (%)	Median (min–max)	0.3 (0.1–0.5)	0.3 (0.2–1.0)	0.010²
Ferritin (ng/mL)	Median (min–max)	53.2 (4.3–298)	105.0 (31–994)	0.001²

AST: aspartate aminotransferase; ALT: alanine aminotransferase; HBV: hepatitis B virus; SD: standard deviation; TIBC: total iron binding capacity.

¹Fisher–Freeman–Halton test (Monte Carlo); ²Mann–Whitney *U* test (Monte Carlo); ³Independent samples *t*-test (Bootstrap). Values in bold indicate statistical significance.

age ($r = -0.203$, $p = 0.003$) and positively with fibrosis stage ($r = 0.225$, $p = 0.025$) and HBV DNA ($r = 0.207$, $p = 0.003$), while no significant correlation was noted between quantitative HBsAg titers and serum iron parameters (Table 4).

Quantitative HBsAg titers were correlated with age negatively in males overall ($r = -0.328$, $p < 0.001$) and positively in females >40 years of age ($r = 0.722$, $p < 0.001$), while no correlation was evident in overall females and in males >40 years of age (Table 4).

In females, quantitative HBsAg titers were positively correlated with fibrosis stage ($r = 0.491$, $p = 0.002$), necroinflammatory grade ($r = 0.235$, $p = 0.049$), and ferritin ($r = 0.288$, $p = 0.011$) regardless of the age, while the positive correlation with HBV DNA ($r = 0.270$, $p = 0.017$) in overall females was not evident when analyzed in those >40 years of age (Table 4).

In males, HBsAg titers were positively correlated with fibrosis stage ($r = 0.501$, $p = 0.003$), necroinflammatory grade ($r = 0.471$, $p = 0.007$), and HBV DNA ($r = 0.313$, $p = 0.012$) as well as with AST ($r = 0.284$, $p = 0.021$) and ALT ($r = 0.265$, $p = 0.031$) only in those >40 years of age (Table 4).

DISCUSSION

Our findings revealed lower levels of serum iron parameters (Fe, ferritin, transferrin saturation) in females

than in males regardless of the age, while no gender influence was noted on fibrosis stage, necroinflammatory grade, HBV DNA, HBeAg status, or quantitative HBsAg titers whether or not stratified by age. No association of quantitative HBsAg titers or HBeAg status was noted with serum iron parameters. However, association of quantitative HBsAg titers with hepatitis parameters and serum ferritin levels significantly varied depending on the age and gender. Accordingly, quantitative HBsAg titers were correlated positively with hepatitis parameters and serum ferritin levels regardless of the age in females, while only for those >40 years of age in males.

Past studies revealed significantly higher levels of serum iron in persistent HBV carriers than those with clearance of the viral infection and higher serum transferrin saturation and ferritin concentrations and increased liver iron deposition in patients with HBV-related liver disease [12, 18–20]. Increase in serum Fe levels has also been associated with increased risk of progression of steatosis to more severe liver pathologies, such as steatohepatitis, fibrosis, and HCC [21–23]. Nonetheless, disturbed iron metabolism in hepatitis is considered to be milder in HBV infection than in HCV infection [24], and in patients without cirrhosis when compared to those with cirrhosis [3, 25–27]. This indicates significant role of iron metabolism in progression to cirrhosis [27, 28] and the role of iron parameters (particularly hepcidin) as a potential biomarker for HBV-related disease surveillance [3].

Table 4: Correlation of quantitative HBsAg with age, fibrosis stage, necroinflammatory scores, and serum iron parameters as stratified by gender and age

	Quantitative HBsAg (IU/mL)									
	All patients (n = 99)		Females (n = 38)		Males (n = 61)		>40 years of age			
	r	p	r	p	r	p	Females (n = 14)		Males (n = 33)	
	r	p	r	p	r	p	r	p	r	p
Age (year)	-0.203	0.003	-0.023	0.840	-0.328	<0.001	0.722	<0.001	-0.148	0.237
BMI (kg/m ²)	-0.101	0.142	-0.121	0.285	-0.106	0.230	-0.133	0.511	0.065	0.598
Serum Fe (µg/dL)	0.041	0.551	0.170	0.135	-0.002	0.980	0.376	0.062	0.116	0.344
TIBC (µg/dL)	-0.024	0.721	0.029	0.801	-0.080	0.364	-0.187	0.352	-0.061	0.620
Transferrin saturation (%)	0.043	0.564	0.121	0.335	0.028	0.772	0.367	0.095	0.144	0.276
Ferritin (ng/mL)	0.111	0.104	0.288	0.011	0.044	0.614	0.560	0.005	0.131	0.285
Fibrosis stage	0.225	0.025	0.491	0.002	0.072	0.583	0.813	<0.001	0.501	0.003
Necroinflammatory grade	0.122	0.095	0.235	0.049	0.061	0.520	0.590	0.026	0.471	0.007
Serum AST (U/L)	0.092	0.181	0.197	0.086	0.062	0.485	0.348	0.087	0.284	0.021
Serum ALT (U/L)	0.101	0.142	0.169	0.141	0.123	0.163	0.271	0.185	0.265	0.031
HBV DNA (IU/mL)	0.207	0.003	0.270	0.017	0.157	0.076	0.209	0.298	0.313	0.012

AST: aspartate aminotransferase; ALT: alanine aminotransferase; BMI: body mass index; HBV: hepatitis B virus; TIBC: total iron binding capacity.

Kendall's tau-b test, Spearman's rho test, r: correlation coefficient. Values in bold indicate statistical significance.

However, data on prevalence and clinical significance of disturbed iron metabolism in patients with HBV-related cirrhosis are relatively scarce, particularly in terms of the relation of changed serum iron markers to HBV infection or to liver injury associated with the chronic HBV infection [15].

In our study, ferritin levels in females were significantly lower than in males and positively correlated with quantitative HBsAg titers. Positive correlation of HBsAg titers with age, fibrosis grade, and ferritin levels but not with HBV DNA in females after 40 years of age seems notable in this regard, emphasizing the likelihood of the more direct role of HBV-related liver injury rather than HBV infection per se to be responsible for alterations in serum iron markers among females [15].

No correlation was noted between serum iron parameters and quantitative HBsAg titers among male patients. However, the titers were positively correlated with HBV DNA, fibrosis stage, and necroinflammatory grade as well as with AST and ALT levels in males after the age of 40 years. This seems notable given the higher levels of serum ALT, iron, and ferritin reported in cirrhotic than in non-cirrhotic patients in a past study along with positive correlation between serum iron parameters and ALT levels only in cirrhotic patients [15]. The concurrence of liver injury and elevated serum iron and ferritin levels was also emphasized, suggesting the liver injury rather than the chronic HBV infection itself to underlie the iron metabolism disorder in cirrhotic HBV-infected patients [15].

In a past study conducted with 976 treatment-naïve CHB patients, HBsAg titers were reported to have poor positive correlation with age [8]. Authors also noted change in HBsAg titers during different phases of HBV infection with higher levels in immune tolerant than in low-replicative phase as well as correlation of baseline HBsAg titers with the serum HBV DNA levels in all the phases [8]. Our findings revealed HBsAg titers to be positively correlated with age but not with HBV DNA in females >40 years of age, while HBsAg titers were not correlated with age but correlated positively with HBV DNA in males >40 years of age. Hence the association between viral load and HBsAg titers was more prominent in younger age for females and in older age for males, when no direct correlation exists between age and HBsAg titers. The variation in the relation between viral load and HBsAg titers depending on age in females and males seems notable given the use of both parameters in patient selection for antiviral treatment and treatment monitoring [7, 8, 29].

Indeed, supporting the positive correlation of HBsAg titers with HBV DNA in our study, a lower HBV DNA level was reported to be the major predictor of HBsAg loss over time in Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus (REVEAL-HBV) study [30]. The low risk of hepatitis relapse in patients with low viral loads has been suggested to lead to a higher chance of HBsAg loss in those with

limited viral replication and persistently normal ALT levels [7].

In addition, HBsAg level, as compared with HBV DNA level, was indicated to serve as a better predictor of HBsAg loss with higher clearance rate of HBsAg in CHB patients with an HBsAg level of <10 IU/mL vs. ≥1000 IU/mL in Elucidation of Risk Factors for Disease Control or Advancement in Taiwanese hepatitis B carriers (ERADICATE-B) study [31].

Recent studies indicate the potential use of quantitative HBsAg to select patients for therapy and to predict and monitor antiviral therapy response in clinical practice, in addition to well-established role of using HBV DNA quantification for this purpose [7, 8, 29]. Our findings emphasized the likelihood of significant gender influence and age dependency on association of quantitative HBsAg titers with ferritin and hepatitis markers, respectively, in CHB patients. This seems notable given the likelihood of combined quantitative assessment of HBV DNA and HBsAg levels to be used to define “minimal-risk” patients with chronic HBV infection for optimal provision of antiviral treatment in clinical practice [7]. Nonetheless, it should be noted that while quantitative HBsAg titers were correlated with serum ferritin levels regardless of the age in females, our findings related to the comparison between men and women >40 years of age to minimize the potential impact of menstrual blood loss of younger women should be interpreted cautiously, given that not all females are menopause after 40 years, and females may also be chronically anemic due to menses.

While no association of HBeAg status was noted with serum iron parameters, HBV DNA levels and necroinflammatory grade were lower and quantitative HBsAg titers were higher in our HBeAg positive versus HBeAg negative patients. This seems notable given that hepatic steatosis and its related metabolic risk factors for progressive liver disease (i.e., ferritin and fasting insulin) have been suggested to contribute to the progression of chronic liver disease in HBeAg-negative asymptomatic HBV carriers with low HBV DNA levels [32].

CONCLUSION

In conclusion, our findings revealed lower serum iron parameters and association of quantitative HBsAg with ferritin levels in females and significant association of quantitative HBsAg with hepatitis markers in females regardless of age and in males after 40 years of age. Our findings also emphasize the likelihood of the more direct role of HBV-related liver injury rather than HBV infection per se in disturbed iron metabolism among female CHB patients and stronger association of HBsAg titers with HBV DNA and liver enzymes in males after 40 years of age. Future studies in larger scale homogenous cohorts are needed to better understand the potential use of HBsAg titers in patient selection and monitoring of antiviral treatment in clinical practice.

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Author Contributions

Nimet Yilmaz – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Hakan Çam – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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