

High incidence of hepatitis B core antibody positivity in metabolic-associated fatty liver disease-related cirrhosis

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Abstract

Background and Aim: The coexistence of metabolic-associated fatty liver disease (MAFLD) in the course of chronic hepatitis B virus infection increases liver-related morbidity. A positive correlation was found between positive hepatitis B core antibody (anti-HBc) and the risk of cirrhosis and hepatocellular carcinoma (HCC) in MAFLD. The relationship between anti-HBc positivity and MAFLD progression to fibrosis, cirrhosis, and liver-related outcomes was determined.

Materials and Methods: This is a retrospective study including 242 patients with biopsy-proven MAFLD, 130 patients with clinically diagnosed MAFLD-related cirrhosis, and 62 patients with MAFLD-related or cryptogenic HCC. Anti-HBc antibody results were compared with clinical outcomes.

Results: Anti-HBc positivity was associated with fibrosis severity ($p=0.005$). Anti-HBc was positive in 19 (20.2%), 33 (25.8%), 53 (35.3%), and 27 (43.5%) patients with F0–F1 fibrosis, F2–F3 fibrosis, cirrhosis (F4), and HCC, respectively. Median steatosis score was grade 3 in anti-HBc positive patients and grade 2 in negative patients ($p=0.07$). Anti-HBc positivity was not associated with significant fibrosis ($\geq F2$), cirrhosis, and any liver related complications including HCC.

Conclusion: Higher anti-HBc positivity was found in MAFLD patients with advanced fibrosis and cirrhosis compared to patients with early stage fibrosis. No relation was found between anti-HBc positivity and development of cirrhosis, HCC or other liver related complications.

Keywords: Anti-HBc; hepatitis B core antibody; MAFLD.

Introduction

Metabolic-associated fatty liver disease (MAFLD) is a new terminology that defines the presence of hepatic steatosis in the course

of metabolic dysregulation. MAFLD is a liver disease representing the hepatic manifestation of a systemic metabolic disorder.^[1,2] It is the most common liver disease with a global prevalence of 25%.^[3] It is also an important etiology for cirrhosis and hepatocellular carcinoma (HCC).^[4]

In chronic Hepatitis B virus (HBV) infection, coexisting MAFLD increases liver-related morbidity and mortality, including HCC.^[5] In the course of chronic HBV infection, several phases were described based on serologic findings. The presence of anti-hepatitis B core antibody (anti-HBc) in the absence of anti-hepatitis B surface antigen (HBsAg) has been defined as HBsAg-negative phase.^[6] In chronic hepatitis C virus (HCV) infection and cryptogenic cirrhosis, concomitant anti-HBc positivity increases the risk of progression to cirrhosis and HCC.^[7] Moreover, a relationship was reported between anti-HBc positivity and progression to cirrhosis and HCC in patients with MAFLD.^[8] However, it has not been confirmed in a different population yet. This study aimed to investigate the relationship between anti-HBc positivity and liver-related outcomes, MAFLD progression to significant fibrosis and cirrhosis.

Materials and Methods

Patients

This study consecutively included patients with biopsy-proven MAFLD ($n=242$), clinically diagnosed MAFLD-related cirrhosis ($n=130$), and MAFLD-related or cryptogenic HCC ($n=62$) who were follow up in the gastroenterology outpatient clinic of two independent tertiary centers. MAFLD diagnosis was established with liver biopsy in patients with past or present metabolic risk factors. Liver biopsy was performed in patients with persistent elevation of aminotransferase levels for at least 6 months, evidence of hepatic steatosis by imaging in the absence of secondary causes of hepatic fat accumulation, and high metabolic burden suggestive of increased risk of advanced liver disease. Patients with significant alcohol consumption, long-term (≥ 3 months) use of a steatogenic medication, viral and autoimmune hepatitis, hereditary hemochromatosis, and alpha1-antitrypsin deficiency were excluded. MAFLD was diagnosed as the presence of at least one the following three parameters in addition to hepatic steatosis; a) overweight or obesity, b) type 2 diabetes mellitus, c) evidence of metabolic dysfunction.^[11] Cirrhosis was diagnosed histologically and/or radiologically and supported by clinical and laboratory findings. The diagnosis of HCC was established according to the European Association for the Study of the Liver Clinical Practice Guidelines.^[6]

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Table 1. Clinical characteristics and laboratory findings of patients with biopsy-proven MAFLD

	Anti-HBc negative	Anti-HBc positive	All	p
n (%)	183 (75.6%)	59 (24.4%)	242	
Female sex, n (%)	80 (44.7%)	27 (45.8%)	107 (44.2%)	0.737
Age (years)	50 (39–57)	51 (47–57)	50 (40–57)	0.06
Body weight (kg)	90 (81–99)	88 (76–99)	90 (80–99)	0.454
BMI (kg/m ²)	32.6 (30.0–35.9)	33.7 (29.0–36.3)	32.8 (29.8–36.1)	0.926
Waist circumference (cm)				
Men	109.0±9.0	110.0±12.3	109.3±9.9	0.860
Women	105.5±10.6	107.3±11.2	106.0±10.8	
Hip circumference (cm)				
Men	108 (104–113)	107 (101–115)	108 (103–113)	0.913
Women	110 (104–116)	113 (104–120)	110 (104–119)	
Diabetes mellitus, n (%)	83 (46.6%)	35 (61.4%)	118 (50.2%)	0.052
Hypertension, n (%)	70 (39.9%)	28 (49.1%)	99 (42.1%)	0.219
Metabolic syndrome, n (%)	125 (68.3%)	40 (67.8%)	170 (68.8%)	0.942
AST (U/L)	41 (30–60)	43 (31–54)	41 (31–58)	0.964
ALT (U/L)	61 (38–98)	63 (38–106)	62 (38–100)	0.844
GGT (U/L)	53 (32–77)	47 (30–78)	50 (31–77)	0.743
Creatinine (mg/dL)	0.78 (0.64–0.90)	0.72 (0.60–0.81)	0.76 (0.63–0.88)	0.021
Fasting glucose (mg/dL)	106 (94–129)	112 (95–136)	107 (95–130)	0.452
HbA1c (%)	5.9 (5.5–6.7)	6.1 (5.8–7.0)	6.0 (5.5–6.8)	0.026
Total cholesterol (mM)	208 (182–239)	199 (162–235)	208 (179–239)	0.118
HDL cholesterol (mM)	45 (39–51)	45 (40–51)	45 (39–51)	0.821
LDL cholesterol (mM)	127 (107–152)	127 (88–155)	127 (103–152)	0.341
Triglycerides (mM)	156 (115–212)	141 (81–220)	151 (110–219)	0.114
Platelet count (×10 ⁹ /L)	228 (197–268)	204 (178–257)	226 (189–265)	0.038
INR	1.02 (0.98–1.07)	1.04 (0.98–1.10)	1.03 (0.98–1.08)	0.202

Continuous variables are presented as mean±standard deviation or median (interquartile range), as appropriate. Anti-HBc: Anti-hepatitis B core antibody; BMI: Body mass index; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transpeptidase; HbA1c: Hemoglobin A1c; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; INR: International normalized ratio; MAFLD: Metabolic-associated fatty liver disease; NASH: Non-alcoholic steatohepatitis.

Data Collections

Clinical and laboratory data were collected retrospectively from the hospitals' electronic database and hardcopy patient files. Aspartate aminotransferase, alanine aminotransferase (ALT), platelets, albumin, sodium, total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, plasma glucose concentration, hemoglobin A1c, prothrombin time, and INR level measurements after overnight fasting were collected. Hepatitis B surface antibody (anti-HBs) and anti-HBc tests were performed via enzyme-linked immunosorbent assays methods. Patients with unknown serological markers of HBV were excluded. Body mass index (BMI) was calculated as patient's weight (in kilograms) divided by the height squared (in meters) and expressed as kg/m². Waist circumference was measured at the superior border of the iliac crest and expressed in cm.

In the MAFLD group, all biopsies were performed using an 18G needle. A single, 20-year experienced, gastroenterology-specific pathologist scored the biopsy specimens. Steatosis, ballooning, lobular inflammation, and fibrosis stages were defined based on the Kleiner system, and steatohepatitis was defined as the presence of hepatic steatosis in >5% of hepatocytes with lobular inflammation and ballooning.^[9] Fibrosis was staged using a 5-tier system, wherein stage 0 indicates

no fibrosis (F0); stage 1, perisinusoidal or portal fibrosis (F1); stage 2, perisinusoidal and portal or periportal fibrosis (F2); stage 3, septal and bridging fibrosis (F3); and stage 4, cirrhosis (F4). Significant and advanced fibrosis was defined as ≥F2 and ≥F3 fibrosis, respectively.

Statistical Analysis

Categorical variables were expressed as frequencies and percentages, and continuous variables were expressed as either mean±standard deviation or median and interquartile range depending on their distributions. Kolmogorov–Smirnov test was used to determine continuous variable distribution. Independent sample t test or Mann–Whitney U test were used to compare continuous variables based on the distribution of variables. Pearson chi-squared test and Fisher's exact test were used to compare categorical variables with respect to the sample size. Binary logistic regression model was used to identify the independent factors associated with significant fibrosis, cirrhosis, and HCC. A two-sided alpha level of <0.05 was accepted as statistically significant.

The study was performed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008 and was approved by the local ethical committee.

Table 2. Histological features of patients with biopsy-proven MAFLD

	Anti-HBc negative	Anti-HBc positive	All	p
n (%)	183 (75.6%)	59 (24.4%)	242	
Steatohepatitis, n (%)	171 (96.6%)	53 (93.0%)	224 (95.7%)	0.263
Steatosis grade	2 (2–3)	3 (2–3)	3 (2–3)	0.040
Lobular inflammation	2 (1–2)	2 (1–2)	2 (1–2)	0.375
Portal inflammation	1 (1–1)	1 (1–1)	1 (1–1)	0.540
Hepatocyte ballooning	1 (1–2)	2 (1–2)	1 (1–2)	0.597
Fibrosis stage	2 (1–3)	2 (1–3)	2 (1–3)	0.155
NAFLD activity score	5 (4–7)	6 (5–7)	6 (5–7)	0.077
Significant fibrosis, n (%)	107 (58.8%)	30 (67.8%)	147 (61.0%)	0.202
Advanced fibrosis, n (%)	59 (32.4%)	22 (37.3%)	81 (33.6%)	0.475
F4 fibrosis, n (%)	12 (6.6%)	7 (11.9%)	19 (7.9%)	0.262

Continuous variables are presented as mean±standard deviation or median (interquartile range), as appropriate. NAFLD: Non-alcoholic fatty liver disease; MAFLD: Metabolic associated fatty liver disease.

Results

The final analysis included 242, 130, and 62 patients with biopsy-proven MAFLD, MAFLD-related cirrhosis, and MAFLD-related or cryptogenic HCC. Anti-HBc and anti-HBs were positive in 30.8% (n=138) and 36.9% (n=140) patients, respectively.

Biopsy-proven MAFLD Cohort

The median age was 50 years (range, 40–57 years), and the median body weight was 90 kg (range, 80–99 kg). Steatohepatitis was diagnosed in 224 (95.7%) patients, and 147 (61.0%) and 19 (7.9%) patients had significant fibrosis and cirrhosis, respectively. Anti-HBc and anti-HBs were positive in 59 (24.4%) and 82 (34.6%) patients, respectively. The cohort consisted of 44.2% female patients, and 50.2% had diabetes. HbA1c was higher and serum creatinine was lower in patients with positive anti-HBc compared with those with negative anti-HBc (6.1% vs 5.9%, $p=0.026$; 0.72 mg/dL vs 0.78 mg/dL, $p=0.021$) (Table 1).

Histological Features

Twenty-nine (12.0%) patients with biopsy-proven MAFLD had no fibrosis, 66 (27.3%) had F1 fibrosis, 66 (27.3%) had F2 fibrosis, 62 (25.6%) had F3 fibrosis, and 19 (7.9%) had F4 fibrosis. In the biopsy-proven MAFLD cohort, 24.4% of patients (n=59) were anti-HBc positive. The advanced fibrosis (\geq F3 on biopsy) rate was higher in the anti-HBc-positive group (67.8% vs 58.8%) but was not statistically significant ($p=0.274$). In addition, the cirrhosis (F4 fibrosis on biopsy) rate was higher in the anti-HBc-positive group (11.9% vs 6.6%) but was not statistically significant ($p=0.171$). The fibrosis stage distribution (F0–F4) was 4 (6.8%), 15 (25.4%), 18 (30.5%), 15 (25.4%), and 7 (11.9%) in 59 patients with positive anti-HBc, and 25 (13.7%), 51 (27.9%), 48 (26.2%), 47 (25.7%), and 12 (6.6%) in 183 patients with negative anti-HBc ($p=0.545$), respectively. Steatosis was more severe in patients with positive anti-HBc (grade 2 vs 3, $p=0.07$). There was no significant difference in lobular inflammation, portal inflammation, hepatocyte ballooning, non-alcoholic fatty liver disease (NAFLD) activity score, and fibrosis among two groups (Table 2).

Cirrhosis and HCC Cohort

The final analysis included 130 patients with clinically diagnosed MAFLD-related cirrhosis, and 62 patients with MAFLD-related or cryptogenic HCC. All patients with HCC had cirrhosis; 42 of those were MAFLD-related, and 20 were cryptogenic.

Of the 192 patients, 51.0% (n=98) were women, 38.0% (n=73) were anti-HBc positive, 59.3% (n=112) had decompensated cirrhosis, and 32.5% (n=62) had HCC. The median cirrhosis duration was 4 years (1–20), and the median Child–Pugh score was 7 (Table 3). Age, sex, BMI, disease duration, comorbidities, and baseline laboratory results were similar between the anti-HBc positive and negative groups. The anti-HBc positive group was not different from the anti-HBc negative group with regards to median model for end-stage liver disease (MELD) score, median Child–Pugh Score, and rates of decompensation, ascites, hepatic encephalopathy, and HCC. However, rate of esophageal varices was significantly higher in the anti-HBc positive group compared to anti-HBc negative group (65.3% vs 50.0%; $p=0.04$).

Anti-HBc Positivity Rates

A positive association was seen between anti-HBc positivity rate and fibrosis severity ($p=0.005$). Anti-HBc was positive in 19 (20.2%), 33 (25.8%), 53 (35.3%), and 27 (43.5%) patients with F0–F1 fibrosis, advanced fibrosis, cirrhosis, and HCC, respectively (Fig. 1).

Anti-HBc and Liver-related Events

The median follow-up time was 4 years (0.5–20) for patients with cirrhosis. Varices, ascites, and hepatic encephalopathy rates were 55.8% (n=106), 43.2% (n=82), and 28.9% (n=55), respectively. In univariate analysis, anti-HBc positivity was associated with the presence of esophageal varices (65.1% vs 49.5%; $p=0.048$) but not with ascites, encephalopathy or overall liver-related complications (Table 3). In multivariate analysis, anti-HBc positivity was not associated with any liver-related complication.

Anti-HBc and HCC

We analyzed 42 and 20 patients with MAFLD-related HCC and cryptogenic HCC, respectively, of which 12 and 15 patients had posi-

Table 3. Clinical characteristics of cirrhosis and HCC cohort

	Anti-HBc negative	Anti-HBc positive	All	p
n	119 (62.0%)	73 (38.0%)	192	
Female sex, n (%)	70 (58.8%)	28 (38.4%)	98 (51.0%)	0.006
Age (years)	60 (53–68)	61 (56–67)	61 (54–67)	0.636
BMI (kg/m ²)	33.2 (20.0–36.7)	30.9 (28.8–34.5)	31.6 (28.0–36.0)	0.160
Cirrhosis duration (years)	4 (3–5)	4 (2–5)	4 (2–5)	0.394
Diabetes mellitus n (%)	84 (71.2%)	48 (65.8%)	132 (69.1%)	0.430
Hypertension, n (%)	45 (38.8%)	29 (39.7%)	74 (39.2%)	0.898
AST (U/L)	37 (27–56)	42 (27–62)	38 (27–59)	0.410
ALT (U/L)	28 (19–42)	30 (22–43)	28 (20–43)	0.348
Total bilirubin (mg/dL)	1.2 (0.8–1.9)	1.2 (0.8–2.2)	1.2 (0.8–2.0)	0.708
Albumin (g/L)	3.7 (3.1–4.1)	3.6 (3.3–4.1)	3.7 (3.1–4.1)	0.927
Creatinine (mg/dL)	0.8 (0.7–1.0)	0.8 (0.7–0.9)	0.8 (0.7–0.9)	0.294
Fasting glucose (mg/dL)	139 (104–187)	124 (105–160)	129 (105–177)	0.38
INR	1.2 (1.1–1.6)	1.3 (1.1–1.5)	1.3 (1.1–1.6)	0.486
Platelet count ($\times 10^9/L$)	98 (72–156)	103 (77–157)	101 (74–156)	0.810
HbA1c (%)	6.8 (5.7–8.3)	6.8 (5.5–8.8)	6.7 (5.6–8.4)	0.820
Child-Pugh score	6 (5–8)	7 (5–8)	7 (5–8)	0.519
MELDNa score	10 (8–16)	11 (9–15)	10 (8–16)	0.391
Decompensation, n (%)	65 (55.6%)	47 (65.3%)	112 (59.3%)	0.187
Ascites, n (%)	48 (40.7%)	34 (47.2%)	82 (43.2%)	0.377
Varices, n (%)	59 (50.0%)	47 (65.3%)	106 (55.8%)	0.040
Hepatic encephalopathy, n (%)	33 (28.0%)	22 (30.6%)	55 (28.9%)	0.703
HCC, n (%)	35 (29.7%)	27 (37.0%)	62 (32.5%)	0.293

Continuous variables are presented as mean \pm standard deviation or median (interquartile range), as appropriate. Anti-HBc: Anti-hepatitis B core antibody; BMI: Body mass index; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; HbA1c: Hemoglobin A1c; INR: International normalized ratio; MELDNa: Model for end-stage liver disease score combined with serum sodium concentration.

tive anti-HBc. Among patients with HCC, those with positive and negative anti-HBc had similar age, sex distribution, prevalence of diabetes and hypertension, anthropometric measurements, and biochemical parameters.

Factors Associated with Development of Significant Fibrosis, Cirrhosis, and HCC

Univariate analysis showed that positive anti-HBc, older age, female sex, diabetes, thrombocytopenia ($<150,000/mL$), and increased ALT levels at diagnosis were associated with significant (F3–F4) fibrosis. Except for female sex, these factors were also associated with cirrhosis. Multivariable analysis showed that older age and thrombocytopenia were independent factors associated with significant fibrosis. In addition to these factors, anti-HBc positivity and increased ALT levels were associated with cirrhosis.

Anti-HBc positivity was not an independent risk factor for development of cirrhosis, HCC or significant fibrosis (Table 4).

Discussion

Anti-HBc positivity has been implicated in causing advanced fibrosis and HCC in patients with cryptogenic cirrhosis and chronic HCV infection.^[10,11] Positive anti-HBc may indicate patients with chronic HBV infection who achieved seroclearance or patients who recov-

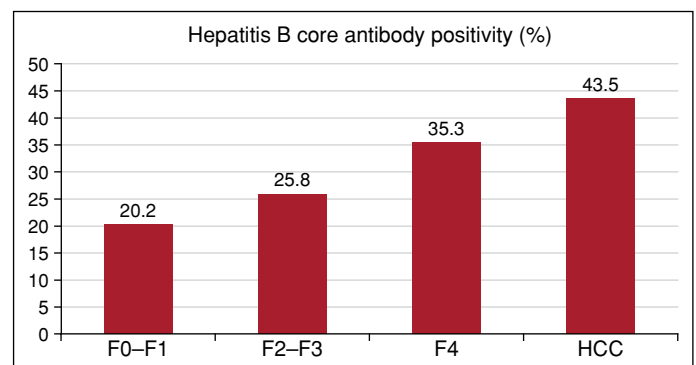


Figure 1. Hepatitis B core antibody positivity rates.

F0: No fibrosis; F1: Perisinusoidal or portal fibrosis; F2: Perisinusoidal and portal or periportal fibrosis; F3: Septal and bridging fibrosis; F4: Cirrhosis; HCC: Hepatocellular carcinoma.

ered from self-limiting acute HBV infection or even occult HBV infection with low copies of HBsAg that could not be detected by commercially available assays.^[12] The most probable contribution of anti-HBc to the development of fibrosis and carcinogenesis is the remaining HBV DNA in hepatocytes. In accordance with this hypothesis, various studies indicate that the majority of patients with chronic HBV infection have detectable HBV genome in the hepatocytes after seroconversion of HBsAg.^[13,14]

Table 4. Factors associated with advanced fibrosis and cirrhosis

	Advanced fibrosis (F3–F4)			Cirrhosis (F4)				
	Univariate analyses	Multivariate analysis		Univariate analyses		Multivariate analysis		
	p*	Coef	OR (95% CI)	p*	p*	Coef	OR (95% CI)	p*
Positive anti-HBc	0.012			0.5430	0.001			0.153
Age at diagnosis	0.000	0.74	1.076 (1.052–1.102)	0.000	0.000	0.072	1.075 (1.047–1.104)	0.000
Female sex	0.012			0.731	0.073			
BMI	0.342				0.877			
Steatohepatitis	0.172				**			
Thrombocytopenia	0.000	0.012	0.988 (0.985–0.991)	0.000	0.000	0.016	0.985 (0.981–0.988)	0.000
AST	0.141				0.502			
ALT	0.000			0.302	0.000	0.023	0.977 (0.968–0.986)	0.000
Metabolic syndrome	0.138				**			
Waist circumference >102 cm for men, >88 cm for women	0.077				**			
Hypertension	0.417				0.247			
Diabetes mellitus	0.000			0.242	0.000			0.447

*: p<0.05 accepted as statistically significant; **: Data not available for patients with clinically diagnosed cirrhosis; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; BMI: Body mass index; HDL: High-density lipoprotein; IFG: Impaired fasting glucose, low-density lipoprotein.

Recently, a study highlighted the importance of anti-HBc in the progression of NAFLD to cirrhosis and HCC.^[8] They found a higher incidence of cirrhosis, HCC, and cirrhotic complications in patients with NAFLD who were anti-HBc positive at a median follow-up of 6 years. Our results showed higher anti-HBc positivity with increasing fibrosis grade, significantly higher rates of anti-HBc in the cirrhotic group and patients with HCC but established no relationship between positive anti-HBc and liver-related complications, including HCC at a median follow-up of 4 years. A prolonged follow-up time may clarify this issue because ascites, the most common complication of cirrhosis, develops approximately in 50% of patients within 10 years after the diagnosis of cirrhosis.^[15]

In our study, in contrast to the previous report, anti-HBc positivity was not found as an independent risk factor for the development of fibrosis and cirrhosis. There may be several reasons for this. First, a distinct prevalence of hepatitis B and anti-HBc positivity were observed in two studies.^[16] The TURHEP study showed 30.6% anti-HBc positivity rate in Turkey.^[17] The estimated anti-HBc positivity rate was approximately 45% in a cohort with similar mean age from China.^[18] Second, heterogeneous clinical implications of the serological term called anti-HBc positivity were noted. These populations may have different rate of chronic HBV infection with seroconversion of HBsAg. Most importantly, the rate of F0 and F1 fibrosis was very low in our biopsy-proven cohort compared with the Chinese cohort (12.0% and 27.3% vs 26.1% and 35.7%, respectively).

Even in the absence of circulating HBV DNA, the integration of HBV DNA in the hepatocyte cell facilitates oncogenesis by production of pro-oncogenic proteins and low-grade hepatic necroinflammation.^[7] Several studies showed an association between anti-HBc and the risk of HCC in cryptogenic cirrhosis and chronic HCV infections.^[10,11] In our study, although patients with HCC had higher anti-HBc positivity than patients with cirrhosis and F0–F3, this difference was not statistically significant. This was not coherent with a previous study and may be due to the low number of patients with MAFLD-related HCC in the study or

predominance of different HBV genotypes with different potentials of carcinogenesis between two countries.

This study has several limitations. First, the HCC group had a relatively small number of patients. Second, it was a retrospective study where-in antibody test results were collected from patients' files. Finally, we lacked HBV DNA levels in the serum or liver tissue of the patients, hence the occult hepatitis B infection rate in our cohort.

In conclusion, higher anti-HBc positivity was found in MAFLD patients with advanced fibrosis and cirrhosis compared to patients with early stage fibrosis. In contrary to the previous report, no relationship was found between anti-HBc positivity and development of cirrhosis, HCC or liver-related complications.

Ethics Committee Approval: The study was in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008 and was approved by the Marmara University Clinical Research Ethics Committee (Approval date: 24.07.2020, approval number: 09.2020.925).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – IE, YY, GA, FG; Design – IE, YY; Supervision – YY; Data Collection and/or Processing – IE, GA, PG, COD, FG; Analysis and/or Interpretation – IE, HTK, COD; Literature Search – IE, YY; Writing – IE, HTK; Critical Reviews – YY, HTK, FG, CAC.

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

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