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CLINICAL MICROBIOLOGY - RESEARCH PAPER

Circulating vascular adhesion protein-1(VAP-1): a possible biomarker for liver fibrosis associated with chronic hepatitis B and C

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Abstract

Vascular adhesion protein-1 (VAP-1) is a multifunctional protein that plays a role in chronic liver diseases and fibrogenesis. The present study aimed to investigate the possible association of VAP-1 levels with the severity of disease progression in chronic hepatitis (CH) B and C patients with differing stages of fibrosis (F0–4), CHB/CHC-related cirrhosis, and hepatocellular carcinoma (HCC). The VAP-1 concentration in patient sera was determined by ELISA. The VAP-1 levels were compared between the F0 group and the F1, F2, F3, F4, cirrhosis, and HCC groups of CHB patients and between the F1 group and the F2, F3, F4, cirrhosis, and HCC groups of CHC patients. The levels of VAP-1 were significantly increased in CHB patients with progressive stages of fibrosis, with the highest concentration being found in those with stage F4 (severe fibrosis). A statistically significant difference was found between F0 and F4 in patients with CHB, but no statistically significant difference was observed between F1 and F4 in patients with CHC. Interestingly, there was no statistically significant difference in VAP-1 levels between patients with cirrhosis and HCC (either CHB or CHC, independently). Moreover, no relationship was found between VAP-1 and ALT levels in either CHC or CHB patients. In general, the VAP-1 levels were significantly higher in CHB than in CHC patients ($P < 0.01$). In conclusion, we suggest that the VAP-1 level may be a noninvasive biomarker for monitoring the severity of fibrogenesis in patients with hepatitis B infection.

Keywords Vascular adhesion protein-1 (VAP-1) · Fibrosis · Chronic hepatitis B · Chronic hepatitis C · Biomarker

Introduction

Hepatitis B and C viruses (HBV/HCV) cause major health problems worldwide. As with other liver diseases, chronic hepatitis (CH) B and C infection results in fibrosis, which can lead to serious complications such as cirrhosis and HCC; however, the risk of developing HCC is higher with these chronic infections as compared with other causes of cirrhosis [1]. Liver inflammation is the most important event in the development of HCC, following which necrosis and fibrosis develop. Fibrosis is the most important pathophysiological indicator of cirrhosis; therefore,

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knowledge of the histological stage of fibrosis has prognostic significance in determining the severity and progression of chronic hepatitis [2]. Biopsy is the standard method for determining fibrosis stage; however, it is an invasive procedure with a risk of complications and is contraindicated in certain patients (those on hemodialysis or with liver abscess), which limits its routine use [3].

Vascular adhesion protein-1 (VAP-1) is a 170-kDa homodimeric sialoglycoprotein that consists of two 90-kDa subunits connected by disulfide bonds [4].VAP-1 can be found in soluble and membrane-bound forms. Membrane-bound VAP-1 has a short cytoplasmic tail, a single transmembrane segment, and a large extracellular domain, the latter of which triggers an inflammatory response by supporting the transmigration and adhesion of leukocytes from vessels to the inflamed region [5].The soluble form of VAP-1, also known as copper-dependent semicarbazide-sensitive amine oxidase (SSAO), is present in human blood. SSOA activity plays a role in the catalysis of oxidative deamination and the conversion of endogenous and exogenous primary amines (creatinine, sarcosine, adrenaline) to aldehydes, thereby releasing cytotoxic products such as ammonia, aldehyde, and hydrogen peroxide (H_2O_2), [6] which can initiate oxidative stress via conversion to hydroxyl radicals and activation of NF-κB-dependent chemokine secretion in the liver endothelium. These products also have insulin-like effects [7].

VAP-1 plays an important role in the pathogenesis of various human diseases including alcoholic liver disease, kidney injury, diabetes, obesity, atherosclerosis, and congestive heart failure [8–10].VAP-1 expressed in peripheral lymph nodes, under both normal and inflammatory conditions, can be found in the sinusoidal and vascular endothelium in the liver [11]. The serum VAP-1 concentration differs among various chronic liver diseases. A previous study examining VAP-1 levels in hepatocellular carcinoma (HCC) resulting from nonalcoholic and alcoholic fatty liver disease showed that the VAP-1 concentration is significantly higher in patients with alcohol-related HCC [12]. Other studies have shown that VAP-1 promotes the progression of steatohepatitis. VAP-1-deficient mice ($AOC3^{-/-}$) have been found to be protected against the development of severe steatohepatitis and the onset of fibrosis, demonstrating that VAP-1 is involved in the pathogenesis of fibrotic liver disease and may be a potential biomarker [13].

In the present study, serum VAP-1 levels were investigated in CHB and CHC patients known to have differing stages of fibrosis, CHB/CHC-related cirrhosis, or HCC. We aimed to show that VAP-1 concentration may be a noninvasive biomarker to demonstrate the progressive fibrosis score in these patient groups.

Materials and methods

Study population

A total of 183 patients diagnosed with CHB ($n = 136$) and CHC ($n = 47$) between March 2016 and September 2018 at the Mersin University Research and Application Hospital Gastroenterology Clinic were retrospectively included in the present study. The number of patients was determined based on the availability of blood samples and the clinical parameters of the patients. The clinical and demographic characteristics of the patients are shown in Table 1.

Determination of fibrosis and VAP-1 levels in patients

Liver biopsies included in the present study were performed by experienced gastroenterologists using standard methods [14]. We divided patients into fibrosis stages according to a modified Ishak model [15]: F0, no fibrosis; F1, fibrous expansion of some portal areas, with or without short fibrous septa; F2, fibrous expansion of most portal areas, with or without short fibrous septa; F3, fibrous expansion of most portal areas with occasional portal-to-portal (P-P) bridging; F4, fibrous expansion of portal areas with marked bridging (P-P as well as portal-to-central (P-C)); F5, marked bridging (P-P and/or P-C) with occasional nodules (incomplete cirrhosis); F6, cirrhosis, probable or definite. According to the biopsy results, 15 CHB and 13 CHC patients were diagnosed with liver cirrhosis (fibrosis stage F5 or F6). In addition, a total of 8 patients with HCC, 4 resulting from CHB and 4 from CHC, were included.

The VAP-1 concentration in patient sera was determined using the R&D Systems Human VAP-1 Quantikine ELISA Kit following the kit protocol. First, 100 μL of assay diluent was added to each well. Then, 50 μL of standard, control, or sample was added to each well and incubated on a microplate shaker for 2 h at room temperature. Each well was aspirated and washed. Furthermore, 200 μL of the conjugate was added to each well and incubated on the shaker for 2 h at room temperature. Each well was aspirated and again washed. Next, 200 μL of substrate solution was added to each well and incubated for 30 min at room temperature. Then, 50 μL of stop solution was added to each well, and the optical density (OD) of each well was measured at 450 nm using a microplate reader.

Determination of HBV DNA, HCV RNA, ALT, and AST levels in patients

Detection of HCV RNA and HBV DNA levels and viral load measurement were performed automatically with the real-time PCR system (COBAS TaqMan 48, Roche) using a TaqMan HCV Test Kit (COBAS AmpliPrep/COBAS TaqMan HCV

Table 1 Patient demographic and clinical information

Range										
	CHB patients ($n = 136$)					CHC patients ($n = 47$)				
	No/mild fibrosis (F0/F1) ($n = 30$)	Moderate fibrosis (F2/F3) ($n = 61$)	Severe fibrosis (F4) ($n = 26$)	Cirr. ($n = 15$)	HCC ($n = 4$)	No/mild fibrosis (F1) ($n = 7$)	Moderate fibrosis (F2/F3) ($n = 19$)	Severe fibrosis (F4) ($n = 3$)	Cirr. ($n = 13$)	HCC ($n = 4$)
Demographic										
Sex (female)	12	25	13	4	–	–	6	1	9	2
Sex (male)	18	36	13	11	4	7	13	2	4	2
Age (years)	25–78 (53.7)	32–88 (55.60)	55–70 (67.40)	53–80 (68.9)	62–81 (69.7)	18–86 (47.71)	21–76 (50.63)	50–77 (66.66)	56–79 (68.07)	60–76 (69.75)
Clinical characteristic										
ALT (IU/I)	9.1–30.2	8.6–49.1	9.9–55.2	15–93	19–37.5	11–175	8–116.4	10–55	17–106.3	15.1–41
AST (IU/I)	13–48	10.3–55	11–48	19–76	33–66	16.1–96	10–103	23–44	23–107.7	29–41
HBV DNA (IU/mL)	< 20–4145	< 20–65,802	< 20–10,377	< 20–441	< 20–1081	-	-	-	-	-
HCV RNA (IU/mL)	-	-	-	-	-	1103–1,292,000	6279–5,001,554	39,777–671,620	22,520–12,416,685	18,220–336,976

Cirr., cirrhosis; *CHB*, chronic hepatitis B; *CHC*, chronic hepatitis C

Test, v2.0) and a TaqMan HBV Test Kit (COBAS AmpliPrep/COBAS TaqMan HBV Test, v2.0), respectively.

ALT and AST levels were detected automatically in a Beckman Coulter AU680 device using an ALT Kit (Beckman Coulter, OSR6107) and an AST Kit (Beckman Coulter, OSR6109), respectively.

Statistical analysis

Statistical analysis was performed with the Statistica package program. The Shapiro–Wilk test was used to test the parameters for normal distribution. The data were found suitable for normal distribution. Mean and standard deviation were used as descriptive statistics. ANOVA was used to check the difference between the groups. Variances were found to be homogeneous. Tukey's test was used for pairwise comparison of the groups, and Dunnett's test was used for comparison with the control group (F0 for CHB; F1 for CHC). In addition, the Student *t* test was used to compare two independent groups. A P value < 0.05 was considered statistically significant.

Results

A total of 183 serum samples were included in the present study, from 136 CHB (117 CHB, 15 cirrhosis, and 4 HCC) and 47 CHC (29 CHC, 13 cirrhosis, and 4 HCC) patients. Demographic characteristics of the patients and clinical data such as liver biopsy results, HBV DNA, HCV RNA, and alanine transaminase (ALT)/aspartate aminotransferase (AST) levels were reviewed (Table 1).

Serum ALT levels in CHB and CHC patients with differing stages of fibrosis according to biopsy results were compared. In CHB patients, there was no statistically significant difference between the different stages of fibrosis in terms of serum ALT levels, for example, F0 (21.7 ± 2.117) vs. F3 (24 ± 2.482) and F0 (21.7 ± 2.117) vs. F4 (21.35 ± 2.384) (P = 0.6302 and 0.9390, respectively). Similar results were found in CHC patients, for example, F1 (51.55 ± 25.62) vs. F4 (28.57 ± 13.57) (P = 0.5698).

In general, VAP-1 concentration was statistically significantly different between CHB and CHC patients (P < 0.01), being significantly higher in the CHB (Table 2; Fig. 1C).

Table 2 Serum VAP-1 concentrations

	Total CHB (n = 136)	Total CHC (n = 47)	P
VAP-1	1955.02 ± 477.89	308.74 ± 364.42	< 0.01

VAP-1, Vascular adhesion protein-1; *CHB*, chronic hepatitis B; *CHC*, chronic hepatitis C

VAP-1 concentrations in CHB patients with differing fibrosis stages according to the biopsy results were compared. There was no statistically significant difference between different stages of fibrosis, for example, F1 vs. F2, F2 vs. F3, and F3 vs. F4 (P > 0.05). Similarly, there was no significant difference between F0 and cirrhosis (P = 1.000) or F0 and HCC (P = 0,281) in terms of VAP-1 concentration. However, stages F4 (severe fibrosis), F3 (moderate fibrosis), F2 (moderate–mild fibrosis), and F1 (mild fibrosis) were statistically significantly different from F0 (no fibrosis) (P < 0.01) (Table 3; Fig. 1A).

VAP-1 concentrations in CHC patients with differing fibrosis stages according to the biopsy results were compared. CHC patients included in the present study had different stages of fibrosis (F1, F2, F3, F4) except F0 (no fibrosis); therefore, VAP-1 concentrations were compared with those in F1 (mild fibrosis). Similar to CHB patients, there was no statistically significant difference between different stages of fibrosis, for example, F2 vs. F3, and F3 vs. F4 (P > 0.05). In addition, there was no significant difference between F1 and cirrhosis (P = 0,913) or F1 and HCC (P = 1.000) in terms of VAP-1 concentration. Unlike patients with HBV, stages F4 (severe fibrosis), F3 (moderate fibrosis), and F2 (moderate–mild fibrosis) were not found to be statistically significantly different from F1 (mild fibrosis) (Table 4; Fig. 1B).

Discussion

VAP-1 plays a critical role in the pathogenesis of inflammatory liver diseases [16]. It is also known to be a biomarker for inflammatory liver diseases. Previous studies have demonstrated that the circulating level of VAP-1 can provide clinical benefit as a noninvasive biomarker to distinguish between simple steatosis and nonalcoholic steatohepatitis (NASH) [12]. Furthermore, several studies have suggested that VAP-1 is a potential therapeutic target for chronic fibrotic liver diseases [13].

In the present study, it is shown that the VAP-1 concentration in the CHB group was significantly elevated at the F1, F2, F3, and F4 stages as compared with that at the F0 stage (Table 3) (Fig. 1A). Previous studies have demonstrated that the serum VAP-1 concentration is higher in hepatic than portal veins in chronic liver diseases, and the VAP-1 concentration increases in hepatic stellate cells with increased fibrosis [17]. Kraemer et al. [18] suggested that the liver parenchyma affected by this condition is also a high source of plasma VAP-1 in CHC patients. We assume that the same is true for CHB patients. The fact that there was a statistical difference in terms of VAP-1 concentration between fibrosis stages F0 and F1, F2, F3, and F4 in patients with CHB supports these findings.

In this study, VAP-1 was associated with progressive fibrosis in patients with CHB. The level of VAP-1 has been shown

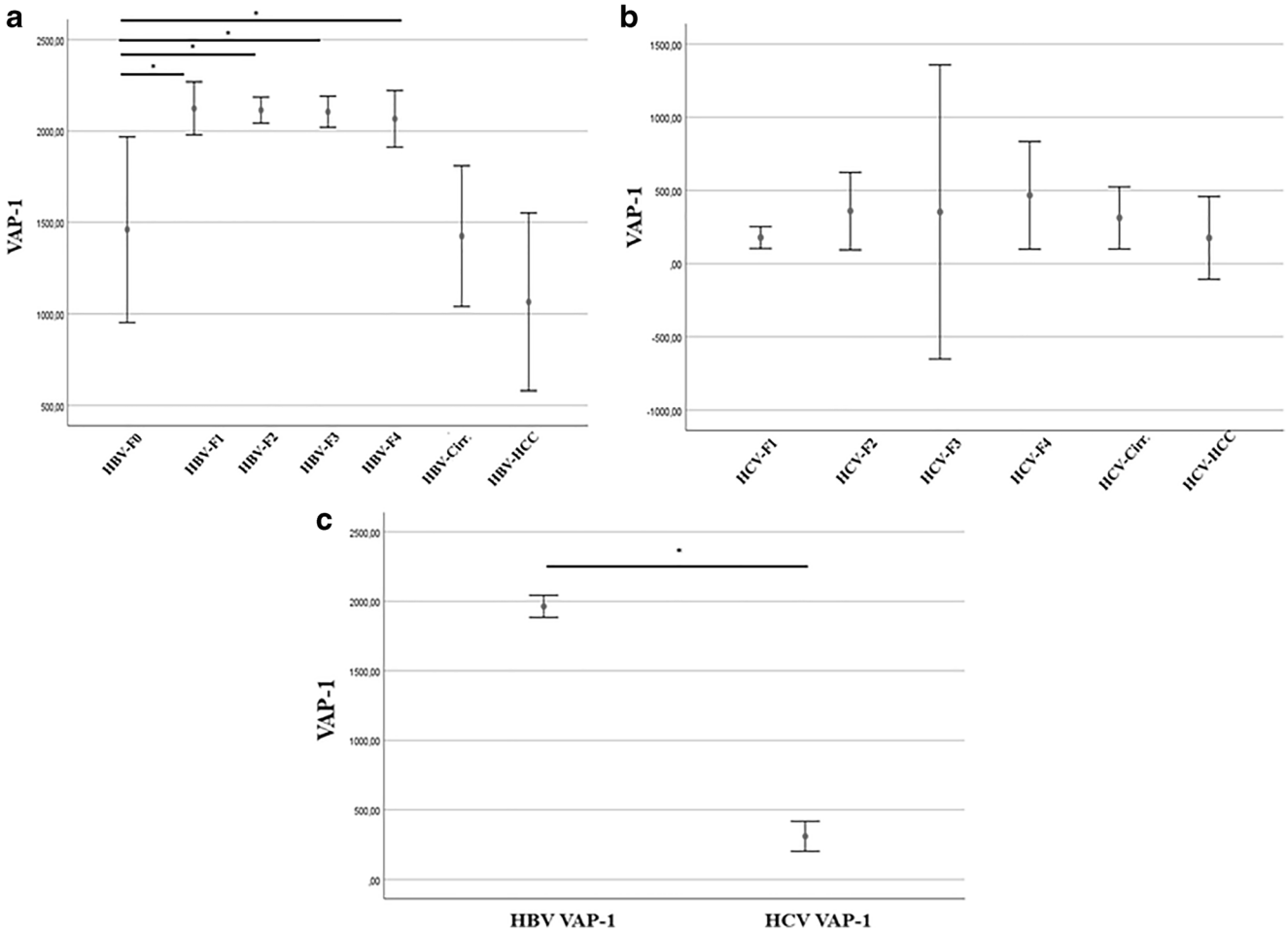

Fig. 1 VAP-1 concentrations at different stages of liver fibrosis. (A) VAP-1 concentration in CHB patients with differing stages of fibrosis, CHB-related cirrhosis, and HCC. F1, F2, F3, and F4 were statistically significantly different from F0 ($P < 0.01$). However, no statistically significant difference was found between F0 and CHB-related cirrhosis ($P = 1.000$) and HCC ($P = 0.281$). (B) VAP-1 concentration in CHC patients with differing stages of fibrosis, CHC-related cirrhosis, and HCC. F2 ($P = 0.745$), F3 ($P = 0.945$), and F4 ($P = 0.712$) were not statistically significantly different from F1. Also, no statistically significant difference was found between F1 and CHC-related cirrhosis ($P = 0.913$) and HCC ($P = 1.000$). (C) Comparison of patients with CHB and those with CHC in terms of the VAP-1 concentration. The difference in VAP-1 levels between patients with CHB and those with CHC was statistically significant ($P < 0.01$). Significance is shown as $^*P < 0.05$

to increase continuously with sustained injury to the liver parenchyma [13]. In addition, four murine hepatic injury models have shown that the elimination or blockade of functional VAP-1 reduces fibrosis [19]. Based on this information and the findings of the present study, we suggest that the VAP-1 concentration was a noninvasive biomarker of progressive fibrosis in patients with CHB.

Unlike patients with CHB, no significant differences were found between the control group (F1) and other fibrosis (F2, F3, and F4) stages in patients with CHC (Table 4) (Fig. 1B). Kreamer et al. [18] investigated the VAP-1 concentration in CHC patients with differing stages of fibrosis and reported that there was no significant difference between the different stages of fibrosis (F0–F1, F2, or F3; F1–F2 or F3 and F2 and

Table 3 VAP-1 levels in F1, F2, F3, F4, cirrhosis, and HCC as compared with F0 in hepatitis B patients

	VAP-1 concentration					
	F1 ($n = 21$)	F2 ($n = 33$)	F3 ($n = 28$)	F4 ($n = 26$)	Cirrhosis ($n = 15$)	HCC ($n = 4$)
F0 ($n = 9$) 1460.36 ± 661.02	2123.98 ± 317.83	2114.80 ± 201,27	2105.71 ± 219.83	2067.26 ± 384.40	1425.18 ± 694.62	1065.27 ± 305.53
P	< 0.01	< 0.01	< 0.01	< 0.01	1.000	0.281

Table 4 VAP-1 levels in F2, F3, F4, cirrhosis, and HCC as compared with F1 in hepatitis C patients

	VAP-1 concentration				
	F2 ($n = 16$)	F3 ($n = 3$)	F4 ($n = 3$)	Cirrhosis ($n = 13$)	HCC ($n = 4$)
F1 ($n = 7$) 177.80 ± 79.92	358.96 ± 496.16	352.32 ± 404.48	466.59 ± 147.76	311.99 ± 349.71	175.37 ± 177.54
P	0.745	0.945	0.712	0.913	1.000

F3), but there was a high degree of difference between F0 and F1 and F4. Our findings are not compatible with the results of this study. However, no statistically significant difference was found between F1 and F4 ($P = 0.712$) in our study (Table 4). This difference might be due to the numerical differences between the CHC patient groups (F1 = 7, F2 = 16, F3 = 3, F4 = 3, Cirr. = 13, and HCC = 4) included in our study. Kreamer et al. [18] included 92 CHC patients with different stages of fibrosis (F0, F1, F2, F3, and F4) in their study. Our study included 47 CHC patients with different stages of fibrosis. This was the limitation of our study in terms of evaluating CHC patient data.

At the same time, the VAP-1 concentration was statistically significantly higher in patients with CHB than in those with CHC (Table 2) (Fig. 1C). The difference in VAP-1 concentration between CHB (136 patients) and CHC (47 patients) may be a result of the different number of patients in each group. Further studies involving more patients are required to clarify the mechanism underlying this difference.

Aminotransferases (ALT/AST) are synthesized in hepatocytes, and the rate of increase in these enzymes is important in determining hepatocellular damage [20]; therefore, the VAP-1 and ALT levels in the included patients were evaluated. However, no statistically significant correlation was found between VAP-1 and ALT levels (CHB or CHC).

Another striking result of our study is the presence of lower VAP-1 concentrations in patients with cirrhosis and HCC as compared with those in CHB and CHC patients at stage F4 (severe fibrosis). At the same time, no statistically significant difference was found between both CHB and CHC control groups (F0 and F1) and cirrhosis and HCC patient groups (Tables 3 and 4). This situation might be due to the low number of patients with cirrhosis and those with HCC in our study, as well as other biological processes underlying the reduction of VAP-1 in cirrhosis and HCC patient groups. Contrary to our findings, Kraemer et al. [18] found that the VAP-1 concentration was high in patients with cirrhosis due to CHC; however, these researchers classed patients with stage F4 fibrosis as having cirrhosis, [21] whereas we classed patients with stage F ≥ 5 fibrosis as having cirrhosis [15]. In our study, in accordance with the findings of these researchers, serum VAP-1 concentrations in F4 patients were high (Fig. 1B, C). Kemik et al. [12] reported that VAP-1 levels are significantly increased in the serum of HCC patients ($n = 55$) whose disease arises from either alcoholic cirrhosis ($n = 33$) or nonalcoholic fatty liver disease ($n = 22$). The same researchers also demonstrated that the VAP-1 concentration is not increased in either CHC- or steatohepatitis-related HCC patients; however, they only mentioned the high VAP-1 concentration in patients diagnosed with steatohepatitis cirrhosis. They reported that the mechanism underlying the difference in the VAP-1 concentration in different liver diseases was uncertain. Our findings are compatible with these results for both CHB- and CHC-related HCC patients. At the same time, Kurkijärvi et al. [22] examined the VAP-1 levels in 41 patients with different liver diseases (ALD, alcoholic liver disease; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; HCC, hepatocellular carcinoma; and CHM, colorectal hepatic metastases). Although some patients with HCC had high levels of VAP-1, this elevation was not statistically significant in general. When evaluated together, it was concluded that serum VAP-1 concentrations were modulated by some inflammatory liver diseases.

The mechanism underlying the difference in VAP-1 concentration among chronic liver diseases remains unclear. The number of patients included in our study (especially those with cirrhosis and HCC) and the difference in patient number among groups are important limitations. Further research is needed, in which deficiencies are eliminated, to clarify the mechanism.

Conclusions Previous studies have shown a relationship between VAP-1 levels and fibrosis severity in patients with CHC [15]; however, to the best of our knowledge, this is the first study to demonstrate a relationship between VAP-1 levels and the severity of fibrosis in patients with CHB. The concentration of VAP-1 increased with the severity of fibrosis in patients with CHB. However, no statistically significant difference was found between patients with CHB/CHC-associated cirrhosis or HCC and the concentration of VAP-1. Hence, it was concluded that VAP-1 concentration, HBV, and HCV could not distinguish patients with no/mild fibrosis (F0, F1) from patients with serious pathologies such as cirrhosis and cancer. More investigation is needed to clarify the underlying mechanism. Although limitations exist due to the limited number of patients in our study, we suggest that VAP-

1 may be a noninvasive biomarker for the detection of progressive fibrosis in CHB patients. In addition, studies involving more patients are required to demonstrate whether VAP-1 is a noninvasive biomarker in determining progressive fibrosis in CHC.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval The study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Mersin University Clinical Research (approval number: 2015/53 for patients with CHB infection and 2017/88 for patients with CHC infection).

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