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Clinical features of hepatitis B and C virus infections, with high α-fetoprotein levels but not hepatocellular carcinoma

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Abstract

The appropriate α-fetoprotein (AFP) level to confirm hepatocellular carcinoma (HCC) could be 100 ng/mL; however, the clinical significance of falsely elevated AFP in patients without HCC has not been fully studied. We investigated the clinical features and outcome of patients without HCC but with high AFP levels (100 ng/mL), especially with chronic hepatitis B (CHB) or C (CHC).

The sample included 124 consecutive patients with CHB (n = 97) or CHC (n = 27), with AFP levels >100 ng/mL and without HCC at baseline. Multivariate Cox proportional regression analysis was performed to determine the factors associated with AFP normalization and HCC development.

During the mean 52-month follow-up, the proportion of patients with CHB with AFP normalization (90.7%) was significantly higher than the proportion of patients with CHC (59.3%, $P < 0.001$). Initial aspartate aminotransferase levels (hazard ratio [HR] = 1.02 per 10 U/L increase, $P = 0.021$) and antiviral therapy (HR = 2.89, $P < 0.001$) were significantly associated with AFP normalization. Of the 16 (12.9%) patients who developed HCC, hepatitis B virus infection (HR = 10.82, $P = 0.001$), initiation of antiviral treatment postenrollment (HR = 0.23, $P = 0.030$), and AFP normalization within 12 months (HR = 0.13, $P = 0.011$) were associated with HCC development.

CHB and CHC were the most common causes of falsely elevated AFP (>100 ng/mL). With either CHB or CHC, persistent AFP elevation (>12 months), regardless of antiviral treatment, might be an important marker of HCC development.

Abbreviations: AFP = α-fetoprotein, ALT = alanine aminotransferase, APRI = aspartate aminotransferase-platelet ratio index, AST = aspartate aminotransferase, CHB = chronic hepatitis B, CHC = chronic hepatitis C, CI = confidence interval, CT = computed tomography, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, HR = hazard ratio, MRI = magnetic resonance imaging.

Keywords: α-fetoprotein, chronic hepatitis B, chronic hepatitis C, hepatocellular carcinoma

1. Introduction

Serum α-fetoprotein (AFP) has served as a diagnostic test for hepatocellular carcinoma (HCC) since the 1970s.[1] Serum AFP is

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also used as a confirmatory test to distinguish HCC from other benign liver lesions, at levels of 200 and 400 ng/mL.[1–4] In previous studies,[5–7] the specificity of 100 ng/mL AFP for HCC was >95%; therefore, even 100 ng/mL could be used to confirm HCC.

However, because of the low sensitivity and high false positive rates, current guidelines do not recommend AFP as a surveillance test for HCC.[8,9] Serum AFP levels can be increased without HCC in patients with hepatitis flare-up or liver cirrhosis.[10,11] In patients with chronic hepatitis C (CHC), this elevation can be associated with liver inflammation and the decline in AFP level during interferon therapy.[12–16] Instead, higher alanine aminotransferase (ALT) and AFP levels postinterferon treatment are associated with the development of HCC.[14] In patients with chronic hepatitis B (CHB), but without HCC, antiviral treatment reduces AFP levels.[17–20] In these studies, HCC developed exclusively in patients with persistently elevated AFP levels after 6[19] or 12 months[18,20] of antiviral therapy. However, most of the patients in these studies had AFP levels <100 mg/mL, which is a level that can be used to confirm HCC.

Although the appropriate AFP level to confirm HCC could be 100 ng/mL, the clinical significance of this AFP level in patients without HCC has not been fully studied. In patients with CHB and HCC, bridging hepatic necrosis on liver biopsy during hepatitis B flare-up is evident in >80% of patients with AFP levels >100 ng/mL; therefore, patients with AFP levels >100 ng/mL

require more aggressive antiviral treatment.[21] In patients with CHC, AFP levels >100 ng/mL are a strong indicator of HCC in hepatitis C virus (HCV)-related cirrhosis, but not for patients with aspartate aminotransferase (AST) levels >80 U/L.[22] Hence, the aims of this study were to investigate the clinical features and outcome of patients without HCC and high AFP levels (100 ng/mL) and to evaluate the predictive factors of AFP normalization and HCC development, especially in patients with CHB or CHC.

2. Materials and methods

2.1. Study population

We retrospectively identified and included 951 consecutive patients age >20 years at Gyeongsang National University Hospital who had high AFP levels (100 ng/mL) between January 2006 and May 2015. We excluded patients with HCC at enrollment (n = 586), with HCC that was diagnosed within 6 months of enrollment (n = 5), with AFP-producing extrahepatic cancer or metastatic liver cancer (n = 94), or who were pregnant (n = 57). We also excluded patients with <6 months of follow-up (n = 72) or incomplete baseline laboratory and image findings (n = 5). Among the remaining 132 patients, patients with etiologies of alcohol (n = 1), drug (n = 5), and hepatitis B virus (HBV) and HCV co-infection were excluded. Finally, 124 patients with CHB (n = 97) or CHC (n = 27) were enrolled (Supplementary Fig. 1, http://links.lww.com/MD/B501). All had available AFP levels and no HCC on imaging, such as ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI), both at enrollment and intervals of at least 6 months. The present study was approved by the Institutional Review Board of the Gyeongsang National University Hospital and is in accordance with the principles of the Declaration of Helsinki 1975.

2.2. Data collection and follow-up

Demographic information, the etiology of liver disease, alcohol consumption, and comorbidities including diabetes, hypertension, and liver cirrhosis were collected. The following clinical and laboratory findings at enrollment were also collected: Child-Pugh score, AST level, ALT level, platelet count, AST-platelet ratio index (APRI), prothrombin time-international normalized ratio, albumin level, bilirubin level, and AFP.

For HCC surveillance, laboratory tests and imaging, including ultrasonography, CT, or MRI, were performed every 3 to 6 months. The cumulative AFP normalization and HCC development rates were measured from the date of enrollment (date of an AFP measurement >100 ng/mL) until the date of death, last follow-up, or study end date (January 31, 2016). In patients with CHB or CHC, antiviral therapy was administered according to the treating physician's decision and Korean Association for the Study of the Liver guidelines.[23,24] The HCC diagnosis was based on histological examinations and/or typical radiographic evidence of hepatic nodules on contrast-enhanced CT or MRI, consisting of hypervascularity in the arterial phase, with washout in the portal or delayed phase.[25] Liver cirrhosis was diagnosed based on evidence of portal hypertension, manifested as varices, splenomegaly, ascites, or hepatic encephalopathy, and compatible imaging findings accompanied by thrombocytopenia.[26] Hepatitis flare was defined as an abrupt elevation of serum AST or ALT to >3× the upper normal limit.[27,28] AFP normalization was defined as AFP levels <20 ng/mL. The APRI was calculated using the AST level and platelet count at baseline.[29]

2.3. Statistical analysis

Continuous variables are expressed as mean ± standard deviation. Between-group differences were evaluated using the Mann–Whitney U test for quantitative data and Fisher exact tests for qualitative data. The probabilities of AFP normalization and HCC development were calculated using the Kaplan-Meier method and compared using the log-rank test. The predictive factors associated with AFP normalization and HCC development were evaluated using univariate and multivariate Cox proportional hazard regression models. The risk is expressed as the hazard ratio (HR) and 95% confidence interval (CI). All analyses were 2-sided, and a P value <0.05 was considered statistically significant. Statistical analyses were performed using PASW software (Version 18, SPSS Inc, Chicago, IL).

3. Results

3.1. Comparison between patients with CHB and CHC

Of the 124 patients, the 97 patients with CHB were significantly younger (mean age, 51.4 years) than the 27 patients with CHC (mean 61.2 years, P < 0.001; Table 1). Significantly more of the patients with CHB were men (68.0% vs 40.7%, P = 0.013). The Child-Pugh score and AST, ALT, and bilirubin levels were significantly higher in patients with CHB than in patients with CHC. The mean AFP level at enrollment in patients with CHB (317.1 ng/mL) was significantly higher than in patients with CHC (177.8 ng/mL, P < 0.001). The proportion of patients with CHB

Table 1

Comparative clinical characteristics between HBV and HCV infected patients with elevated AFP levels (n = 124).

Variables	HBV (n = 97)	HCV (n = 27)	P
Age, y	51.4 ± 10.4	61.2 ± 10.8	<**0.001**
Gender, male	66 (68.0%)	11 (40.7%)	**0.013**
Liver cirrhosis	48 (49.5%)	13 (48.1%)	1.000
Alcohol > 80 g/d	10 (10.3%)	3 (11.1%)	1.000
Diabetes	13 (13.4%)	4 (14.8%)	1.000
Child-Pugh score	6.7 ± 2.1	5.7 ± 1.2	**0.020**
APRI at enrollment	5.7 ± 6.6	2.8 ± 2.0	0.101
AST at enrollment, U/L	270.9 ± 327.3	113.1 ± 62.6	**0.020**
ALT at enrollment, U/L	284.9 ± 377.3	113.1 ± 62.6	**0.001**
PT-INR at enrollment	1.31 ± 0.39	1.21 ± 0.20	0.412
Albumin at enrollment, g/dL	3.4 ± 0.6	3.6 ± 0.4	0.104
Bilirubin at enrollment, g/dL	3.3 ± 4.4	1.3 ± 0.8	**0.002**
Platelet at enrollment, ×1000/μL	133.8 ± 58.9	117.2 ± 50.3	0.211
AFP at enrollment, ng/mL	317.1 ± 405.8	177.8 ± 66.5	<**0.021**
Peak AFP, ng/mL	6711.4 ± 61,391.1	466.4 ± 1288.8	0.598
AFP normalization during study period	88 (90.7%)	16 (59.3%)	<**0.001**
AFP normalization within 3 mo	14 (14.4%)	2 (7.4%)	0.519
AFP normalization within 6 mo	43 (44.3%)	3 (11.1%)	**0.001**
AFP normalization within 9 mo	67 (69.1%)	6 (22.2%)	<**0.001**
AFP normalization within 12 mo	76 (78.4%)	8 (29.6%)	<**0.001**
Hepatitis flare*	62 (63.9%)	11 (40.7%)	**0.046**
Antiviral treatment after enrollment	76 (78.4%)	8 (29.6%)	<**0.001**
Developed HCC	12 (12.4%)	4 (14.8%)	0.749
Death	10 (10.3%)	2 (7.4%)	1.000
Follow-up period	52.7 ± 33.5	49.7 ± 33.6	0.667

Data are presented as mean ± standard deviation for continuous data and number (%) for categorical data.

AFP = α-fetoprotein, ALT = alanine aminotransferase, APRI = aspartate aminotransferase-platelet ratio index, AST = aspartate aminotransferase, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, PT-INR = prothrombin time-international normalized ratio.

* Defined as a >3-fold increase in the upper limit of normal serum AST or ALT level.
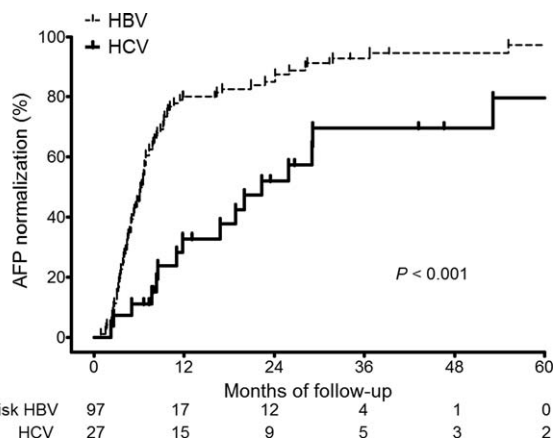
Figure 1. Cumulative probability of AFP normalization between patients with CHB and CHC (*P* < 0.001). AFP normalization is significantly more probable among patients with CHB than among those with CHC. AFP = α-fetoprotein, CHB = chronic hepatitis B, CHC = chronic hepatitis C, HBV = hepatitis B virus, HCV = hepatitis C virus.

and hepatitis flare at baseline was higher (63.9%) than that of patients with CHC (40.7%, *P* = 0.046).

During the mean follow-up of 52 months, antiviral therapy was initiated in 76 (78.4%) patients with CHB and 8 (29.6%) patients with CHC (*P* < 0.001). Of the 124 patients, 12 (12.4%) patients with CHB and 4 (14.8%) patients with CHC developed HCC during the study period (*P* = 0.749). Moreover, 10 (10.3%) patients with CHB and 2 (7.4%) patients with CHC died during the study period (*P* = 1.000).

3.2. Changes in AFP levels during the study period

The proportion of patients with CHB who experienced AFP normalization during the study period (90.7%) was significantly higher than of patients with CHC (59.3%, *P* < 0.001). In addition, the proportion of patients with CHB who experienced AFP normalization within 6, 9, and 12 months was significantly higher than that of patients with CHC; the same was not true for AFP normalization within 3 months (Table 1). Figure 1 compares the cumulative probability of AFP normalization between patients with CHB and CHC (*P* < 0.001). Of the 124 patients, the cumulative probabilities of AFP normalization in patients with CHB or CHC at 1 year were 80.1% and 32.8%, respectively, and the cumulative probabilities of AFP normalization in CHB or CHC patients at 3 years were 94.6% and 69.5%,
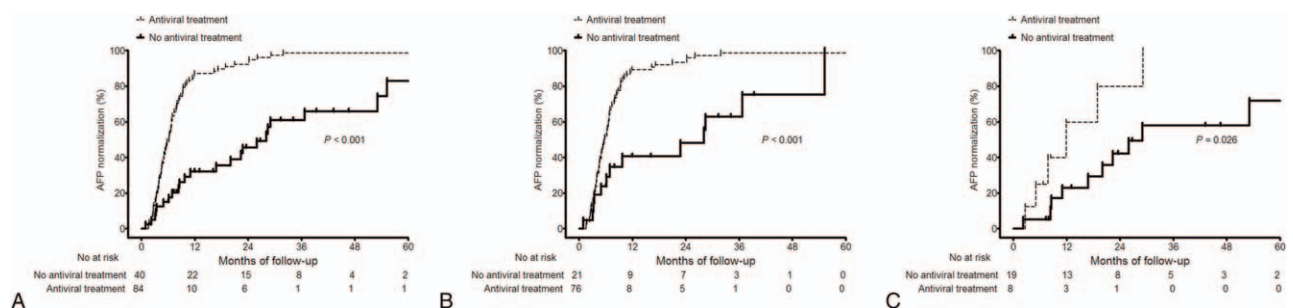
respectively. Figure 2 shows the cumulative probability of AFP normalization according to the initiation of antiviral treatment after enrollment. Of the 124 patients, the cumulative probability of AFP normalization in patients who received antiviral therapy was significantly higher than in patients who did not receive antiviral treatment (*P* < 0.001). There were significant differences in rate of AFP normalization in the 97 patients with CHB (*P* < 0.001) and 27 patients with CHC (*P* = 0.026) between with and without antiviral treatment, respectively.

In the univariate Cox regression analyses, age, HBV infection, initial AFP level, initial AST level, initial ALT level, antiviral therapy, APRI, and hepatic flare were significantly associated with AFP normalization (Table 2). In the multivariate analysis, initial AST level (HR = 1.02 per 10 U/L increase, 95% CI = 1.00–1.04, *P* = 0.021) and antiviral therapy (HR = 2.89, 95% CI 1.66–5.01, *P* < 0.001) were significantly associated with AFP normalization.

3.3. Development of HCC during the study period

Of the 124 patients, 16 (12.9%) patients developed HCC during the observation period, and the cumulative probability of AFP normalization in patients who did not develop HCC was significantly higher than that in patients who did develop HCC (*P* < 0.001, Supplementary Fig. 2A, http://links.lww.com/MD/B501). There was a significant difference in the rate of AFP normalization based on HCC development in the 97 patients with CHB (*P* < 0.001, Supplementary Fig. 2B, http://links.lww.com/MD/B501), but not in the 27 patients with CHC (*P* = 0.077, Supplementary Fig. 2C, http://links.lww.com/MD/B501). Among the 76 patients with CHB who received antiviral therapy, the probability of AFP normalization in patients who did not develop HCC was higher than in patients who developed HCC (*P* = 0.031, Supplementary Fig. 3A, http://links.lww.com/MD/B501). Among the 21 patients with CHB who did not receive antiviral therapy, the probability of AFP normalization in patients who did not develop HCC was higher than in patients who did develop HCC (*P* = 0.008, Supplementary Fig. 3B, http://links.lww.com/MD/B501).

In the univariate Cox regression analyses, age, initial AST level, initial ALT level, antiviral therapy, and AFP normalization within 12 months were significantly associated with HCC development (Table 3). In the multivariate analysis, HBV infection (HR = 10.82, 95% CI = 2.49–47.06, *P* = 0.001), antiviral therapy after enrollment (HR = 0.23, 95% CI = 0.06–0.87, *P* = 0.030), and AFP normalization within 12 months (HR = 0.13, 95% CI = 0.03–0.62, *P* = 0.011) were significantly associated

Figure 2. Kaplan–Meier survival curves according to the initiation of antiviral treatment. The cumulative probability of AFP normalization in all 124 patients (A), 97 patients with chronic hepatitis B (B), and 27 patients with chronic hepatitis C (C). AFP = α-fetoprotein.

Table 2

Univariate and multivariate analyses of the predictors of AFP normalization (n = 124).

Variables	Univariate analysis		Multivariate analysis	
	P	HR (95% CI)	*P*	HR (95% CI)
Age, y	**0.001**	0.97 (0.96–0.99)	0.614	0.99 (0.97–1.02)
Gender, male	0.176	0.13 (0.88–1.98)		
HBV infection	<**0.001**	0.29 (1.71–5.04)	0.163	1.55 (0.83–2.87)
Cirrhosis	0.248	0.80 (0.54–1.17)		
Alcohol > 80 g/d	0.605	1.17 (0.64–2.15)		
Initial AFP (per 100 mg/dL increase)	**0.017**	1.07 (1.01–1.12)	0.719	1.01 (0.94–1.09)
Initial AST (per 10 U/L increase)	<**0.001**	1.02 (1.01–1.03)	**0.021**	1.02 (1.00–1.04)
Initial ALT (per 10 U/L increase)	<**0.001**	1.01 (1.01–1.02)	0.349	0.99 (0.98–1.01)
Antiviral treatment	<**0.001**	3.97 (2.44–6.46)	<**0.001**	2.89 (1.66–5.01)
APRI	<**0.001**	1.05 (1.03–1.08)	0.551	0.98 (0.93–1.04)
Hepatitis flare[*]	**0.002**	1.88 (1.16–2.81)	0.800	1.06 (0.66–1.73)

AFP = α-fetoprotein, ALT = alanine aminotransferase, APRI = aspartate aminotransferase-platelet ratio index, AST = aspartate aminotransferase, CI = confidence interval, HBV = hepatitis B virus, HR = hazard ratio.
[*] Defined as a >3-fold increase in the upper limit of normal serum AST or ALT level.

Table 3

Univariate and multivariate analyses of the predictors of HCC development in patients with elevated AFP levels (n = 124).

Variables	Univariate analysis		Multivariate analysis	
	P	HR (95% CI)	*P*	HR (95% CI)
Age, y	**0.001**	1.09 (1.04–1.15)	0.186	1.05 (0.98–1.13)
Gender, male	0.682	0.81 (0.29–2.23)		
HBV infection	0.693	0.80 (0.26–2.47)	**0.001**	10.82 (2.49–47.06)
Cirrhosis	0.108	2.34 (0.83–6.59)		
Alcohol > 80 g/d	0.686	0.66 (0.09–4.99)		
Initial AFP (per 100 mg/dL increase)	0.087	0.58 (0.32–1.08)		
Initial AST (per 10 U/L increase)	**0.027**	0.92 (0.85–0.99)	0.083	0.89 (0.78–1.02)
Initial ALT (per 10 U/L increase)	**0.031**	0.92 (0.86–0.99)	0.898	1.01 (0.91–1.11)
Antiviral treatment	**0.003**	0.20 (0.07–0.58)	**0.030**	0.23 (0.06–0.87)
Child-Pugh score	0.502	0.92 (0.72–1.17)		
APRI	0.182	0.89 (0.74–1.06)		
Hepatitis flare[*]	0.081	0.41 (0.15–1.12)		
AFP normalization within 12 mo	<**0.001**	0.08 (0.02–0.28)	**0.011**	0.13 (0.03–0.62)

AFP = α-fetoprotein, ALT = alanine aminotransferase, APRI = aspartate aminotransferase-platelet ratio index, AST = aspartate aminotransferase, CI = confidence interval, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HR = hazard ratio.
[*] Defined as a >3-fold increase in the upper limit of normal serum AST or ALT level.

with HCC development. In the Kaplan-Meier analysis, the cumulative probability of developing HCC was significantly higher in patients without AFP normalization within 12 months than in those with AFP normalization within 12 months (Fig. 3A), and it was significantly higher in patents without antiviral treatment after enrollment than in those with antiviral treatment after enrollment (Fig. 3B).

Among the patients with AFP normalization in 12 months, 3 developed HCC; all of these patients had HBV infection and treatment initiation with an antiviral agent at enrollment. They developed HCC at 78.6, 75.9, and 44.8 months after enrollment and initiation of antiviral treatment (lamivudine, clevudine, and entecavir, respectively). However, none of the 8 patients with CHC with AFP normalization in 12 months developed HCC, and
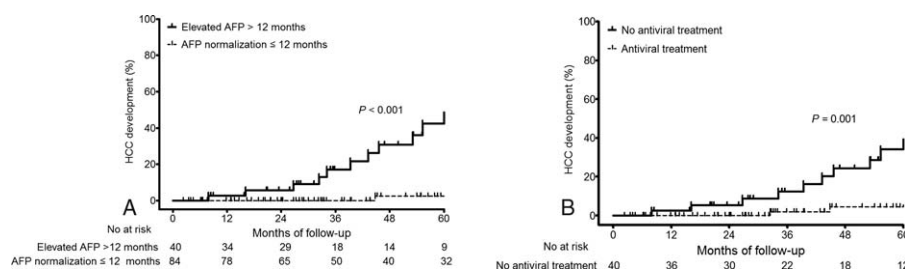
Figure 3. Cumulative probability of HCC development. The cumulative probability of developing HCC is significantly higher in patients without AFP normalization within 12 months (A) and in patients without antiviral treatment (B). AFP = α-fetoprotein, HCC = hepatocellular carcinoma.

4 of these patients received antiviral therapy with peg-interferon and ribavirin and achieved sustained virologic response.

4. Discussion

In our retrospective, observational study of patients with elevated AFP levels and without evidence of HCC at baseline, 97 patients with CHB and 27 patients with CHC had high AFP levels (100 ng/mL). The initial AST, ALT, and bilirubin levels in patients with CHB were higher than those in patients with CHC. Although the baseline AFP level was higher in patients with CHB than in patients with CHC, significantly more of the patients with CHB experienced AFP normalization during the study period. Initial AST levels and antiviral therapy were significantly associated with AFP normalization. Of the 124 patients, 16 (12.9%) patients developed HCC, and HBV infection, initiation of antiviral treatment after enrollment, and AFP normalization within 12 months were independent factors for HCC development.

During the period of observation, 7 patients were excluded for alcoholic hepatitis (n = 1), drug-induced liver injury (n = 5), and HBV and HCV co-infection (n = 1), despite high AFP levels (100 ng/mL). Thus, falsely elevated AFP levels (>100 ng/mL) were caused most often by HBV and HCV infection. In patients with CHB, elevated AFP levels were not persistent and were consistent with serum ALT levels and the presence of bridge fibrosis in >80% of patients with AFP levels >100 ng/mL.[21] Antiviral therapy can reduce not only HBV activity but also falsely elevated AFP levels in patients with CHB.[18–20] The reported prevalence of elevated AFP in CHC ranges from 10% to 43%.[30–32] In addition to the association between AFP elevation and liver inflammation and a decrease in AFP levels during interferon therapy in patients with CHC,[12–15] patients with CHC usually have mild hepatic necroinflammatory activity and a low degree of fibrosis, resulting in mildly elevated ALT levels, unlike patients with CHB.[33] In the present study, AST, ALT, and bilirubin levels in patients with CHB were higher at enrollment than in patients with CHC.

In the present study, although baseline AFP levels in patients with CHB were higher than those in patients with CHC, the proportion of patients with CHB who experienced AFP normalization during the study period was significantly higher than that of patients with CHC. In patients with CHC, elevated AFP levels decrease during interferon therapy.[12–15] Similarly, nucleos(t)ide analog treatment reduces AFP levels in patients with CHB.[17–20] In the present study, the cumulative probability of AFP normalization in patients undergoing antiviral therapy was higher than that in patients without antiviral treatment. In addition, there were significant differences in the rate of AFP normalization based on antiviral treatment with both CHB and CHC. At 12 months after enrollment, the mean ALT levels were significantly lower than the baseline ALT levels (240.9–38.34 U/L, $P < 0.001$). These results are similar to those of previous studies.

AFP normalization within 12 months was an independent factor for HCC development after adjusting for potential confounding variables in the present study. In particular, AFP levels in 76 (78.4%) of patients with CHB were normalized (<20 ng/mL) within 12 months after enrollment. The proportions of patients with CHB who experienced AFP normalization within 12 months were 89.5% with antiviral treatment and 40.6% without antiviral treatment. In contrast, only 8 (29.6%) of the patients with CHC had AFP levels <20 ng/mL in 12 months. The proportions of patients with CHC who experienced AFP normalization within 12 months were 60% with antiviral treatment and 23% without antiviral treatment. We showed that the AFP level at 12 months in patients with high AFP levels (100 ng/mL), but not HCC, at baseline was a potential predictor of developing HCC not only for patients with CHB but also for patients with CHC.

To the best of our knowledge, no previous observational study of the clinical features and outcome of patients without HCC and with high AFP levels (100 ng/mL) that could be used to confirm HCC has been conducted, especially in patients with CHB or CHC. However, our study had several limitations, including the retrospective design and relatively small sample size from a single center. Additionally, there were a number of different antiviral agents used, including lamivudine, adefovir, clevudine, entecavir, telbivudine, tenofovir, and interferon and ribavirin.

In conclusion, most of the patients without HCC but with high AFP levels (100 ng/mL) had either CHB or CHC. Persistent (>12 months) AFP elevation might serve as an indicator of HCC development, regardless of antiviral treatment. Therefore, larger multicenter studies are needed to elucidate the predictors for HCC development in patients without HCC and a high AFP level.

Acknowledgments

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