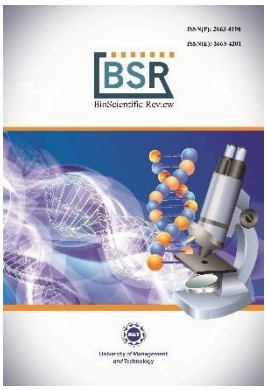

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The Correlation between Alpha-fetoprotein and Liver Function Tests

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Abstract

Serum alpha-fetoprotein (AFP) level is a good indicator of important pathological stages in patients with chronic liver diseases. This study aims to investigate the alpha-fetoprotein level in male and female patients and to correlate it with other liver functions tests (LFTs), such as ALT, AST, total albumin and total protein. A total of 100 patients within the age range 20-85 years who visited Shaukat Khanum Laboratory in Lahore were recruited for this study. Automated chemiluminicence microparticle immuno assay and immulite 2000 (CMIA, siemens USA) were used to measure serum AFP level. To measure serum ALT and AST, Architect 8200 kit (Abbott, USA) was used with a reference range of 0-50 U/L, according to the manufacturer's protocols. Out of the total 100 samples (55 males, 45 females), 47 samples (47%) had normal AFP level (<5IU/l) and 53 samples (53%) had high AFP level (>5IU/l). A higher frequency of elevated AFP was observed in men at 60.38%. There was no significant correlation of AFP level with ALT (p= 0.38, r2= 0.002), T.P. (P. value= 0.7635 r2= 0.002) and albumin levels (p= 0.07, r2 =0.041). However, a significant correlation was found between AFP and AST levels (p= 0.02, r2= 0.15). Our study found a higher AFP level in older population (>60) as compared to the younger people (20-40) and a higher frequency among males (60.38%) as compared to females (39.63%). It also found that AFP level significantly correlates with AST level but does not show any association with ALT and albumin levels.

Abbreviations: alanine transaminase (ALT), aspartate transaminase (AST), hepatocellular carcinoma (HCC), hepatitis B virus (HBV), hepatitis C virus (HCV), liver function tests (LFTs)

1. Introduction

Alpha-fetoprotein (AFP), a fetal antigen, is a glycoprotein produced in yolk sac and liver during embryonic stages and it reaches the maximum concentration of 3g/l in 12-16 weeks of gestation. By the age of 8-12 months, its level decreases to 10 ug/l and continues to decrease until its normal adult level is achieved. However, its elevated levels have been reported in hepatocellular carcinoma (HCC), various

liver diseases, metabolic syndrome and germ cell cancers [1, 2, 3, 4]. The elevated serum AFP level in HCC is concomitant with tumor burden, poor differentiation, tumor recurrence and growth and proliferation of hepatoma cells in humans [5, 6, 7]. Currently, AFP is the most widely tested tumor biomarker in HCC [8]. However, the test performance of AFP varies in detection and surveillance of HCC due to a multitude of reasons. This variability can be attributed to variance in study design, demographics of sample, underlying etiology of liver diseases such as viral hepatitis, and the concentration of AFP [9, 10]. The concentration of AFP is reportedly associated with tumor size, thereby making it a suitable marker for the detection of advanced tumors, plummeting its role in surveillance [8]. Also, patients with HCV and HBV show a raised AFP level which could serve as a predictive marker for the development of HCC [11, 12].

Hepatic markers are used at many levels of HCC diagnosis and prediction. Aspartate transaminase (AST) and alanine transaminase (ALT) are enzymes produced by liver and are used as sensitive markers in liver function tests (LFT) along with alkaline phosphatase (ALP), total protein, bilirubin and albumin [13]. The patients of chronic hepatitis B and C are reported to have elevated concentrations of AFP along with hepatic cytolysis markers AST and ALT [14, 15, 16]. Elevated AFP and aminotransferases are associated with poor prediction of HCC. Taking into consideration the change in AST or ALT level in a specified time frame helps in better prediction by algorithms based on serum AFP level for diagnosis and surveillance of HCC [17]. Normal liver synthesizes albumin, a protein which is an indicator of normal liver functioning. Albumin level falls with progressive liver diseases and therefore serves as a prognostic marker of chronic liver diseases [18]. Any prediction and risk assessment of HCC based on AFP alone reportedly has low sensitivity and potentially missed cases due to positive predictive value. Adding other factors into the algorithm such as platelets and ALT can increase its efficacy [19].

The evaluation and prediction of LFTs and AFP is complicated as various hepatic diseases, carcinoma, viruses, metabolism and several other factors have a role in the final outcome. In this study, we aimed to determine the AFP level in male and female patients and any correlation between AFP and LFTs. This may help to increase the diagnostic efficacy of HCC by better interpretation of algorithms used for serum AFP level.

2. Methodology

2.1. Sample Collection

The aim of this cross-sectional study was to determine the AFP level in patients suspected with HCC and to find the correlation between AFP and LFTs (ALT, AST, total albumin and total protein). Blood samples were collected through venipuncture from 100 patients within the age range of 20-85 years, who visited Shaukat Khanum Laboratory in Lahore from September 2018 to July 2019. Individuals with an elevated level of alpha-fetoprotein (AFP) were included in the study after initial screening. Those with elevated AFP were further checked for ALT, AST, total albumin and total protein. Patients with a normal AFP level were excluded from the study. Selected patients were than classified according to age and gender.

2.2. Test Method

The venous blood was kept at room temperature for 1 hour prior to

centrifugation at 3000 r/min for 10 minutes. Serum was collected and stored at -20 ^{0}C untill use. Serum AFP level was estimated using automated chemiluminicence microparticle immuno assay technology and immulite 2000 (CMIA) by Siemens, US. The range of normal reference value for AFP is <5 IU/L. Serum ALT and AST were estimated using kits of Architect 8200 by Abbott (USA) at the reference range of 0-50 U/L, according to the manufacturer's guide. Serum total protein and serum albumin levels were detected with kits of Architect 8200 by Abbott (USA) at the reference range of 5.5-8.0 mg/dl and 3.5-5.5mg/dl, respectively. The operational guidelines provided in the reagent manual for test procedures were strictly followed for all reagents and tests.

2.3. Statistical Analysis

Statistical analysis was performed using SPSS 21.0 statistical software. Numerical data were expressed as frequency and/or percentage (%). Correlation analysis was carried out through linear regression using Pearson correlation coefficient. Differences with *p* value less than 0.05 were considered statistically significant.

3. Results

A total of 100 blood samples were screened for the concentration of AFP (n= 100), out of which 55 (55%) were of males and 45 (45%) were of females (Figure 1). 47 samples (47%) had normal AFP level (<5IU/l), whereas 53 samples (53%) had high AFP level (>5IU/l) (Figure 1). The age wise and gender wise distribution of normal and high levels of AFP is shown in Table 1. In this study, a higher frequency of elevated AFP level (60.38%) was reported for men as compared to women (39.63%). The age distribution and frequency of AFP within and across gender is shown in Fig. 2. One notable observation is the high frequency of both normal AFP and high AFP concentrations in age group 41-60 for women as compared to any other age group for women (57.14%), whereas for men the highest frequency was recorded in age group >60 (50%) (Fig. 2). Moreover, no case with high AFP level was recorded in age group 20-40 among females. Furthermore, this study found a higher AFP level in the older population (>60) as compared to in younger people (20-40).

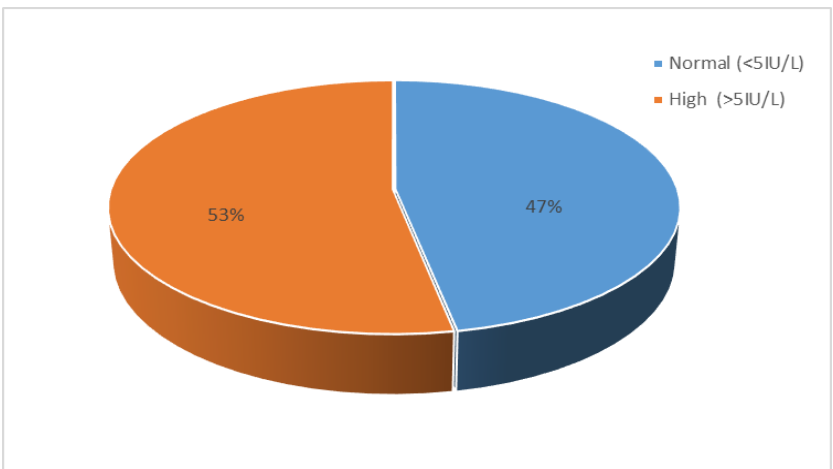

Figure 1. Frequency of normal and high alpha-fetoprotein level

The nature of association between AFP and ALT, AST, T.P. and albumin was evaluated. It was found that AFP level did not correlate with ALT (p= 0.38, r^2= 0.002), T.P. (*P*. value= 0.7635 r^2= 0.002) and albumin (p= 0.07, r^2 =0.041) levels. However, it did significantly correlate with AST level (p= 0.02, r^2= 0.15) (Figure 3.B). All markers showed a negative correlation with AFP.

Table 1. The Distribution of Alpha-fetoprotein Level by Gender and Age in the Studied Population

Gender	AFP-level	20-40		41-60		>60		Total N=100
		n	%	N	%	n	%	%
Female	Normal	5	20.84	13	54.17	6	25	24
	High	0	0	12	57.14	9	42.86	21
Male	Normal	1	4.35	15	65.21	7	30.44	23
	High	4	12.5	12	37.5	16	50	32

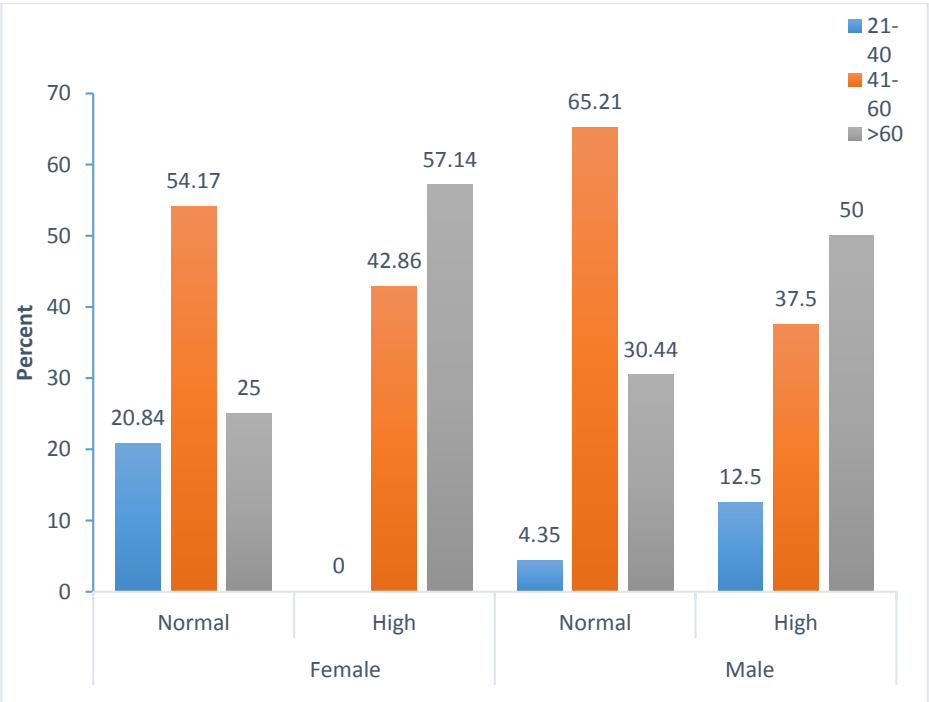

Figure 2. Frequency of normal and high alpha-fetoprotein level across gender and age groups. The frequency of elevated AFP level for men (60.38%) is higher as compared to women (39.63%)

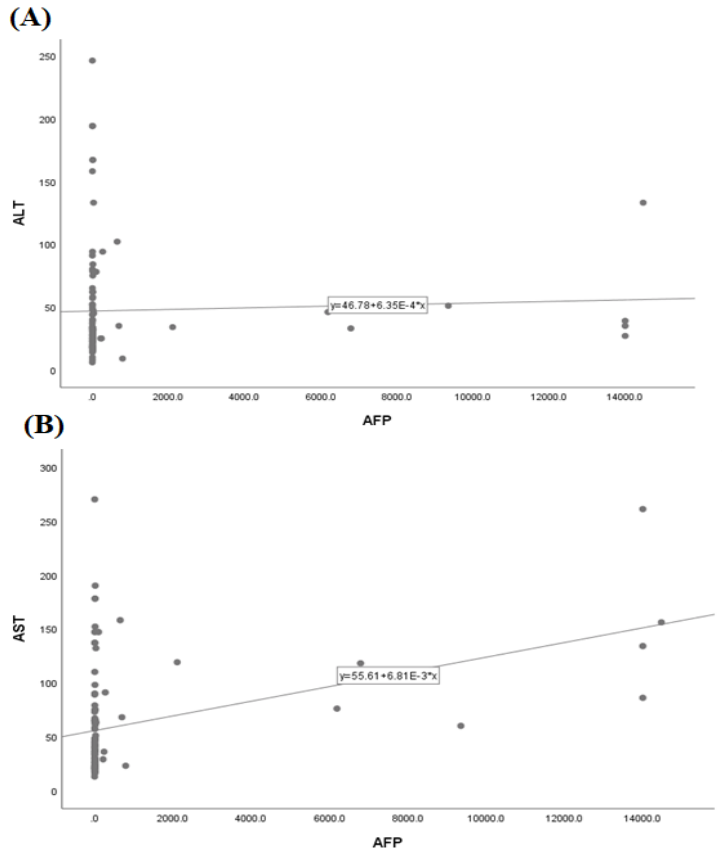

Figure 3. The graph shows Pearson correlation between (A). alpha-fetoprotein and alanine aminotransferases. AFP is shown on *x*-axis and ALT on *y*-axis. There is no significant (p= 0.38) correlation between AFP and ALT (r^2= 0.002). (B). Alpha-fetoprotein and aspartate aminotransferases. *X*-axis shows AFP and *y*-axis shows AST. There is a significant correlation between AFP and AST (p= 0.021, r^2= 0.15). P < 0.05 is considered as significant for each association

4. Discussion

Serum AFP is the most widely used tumor biomarker for HCC. We screened 100 individuals who were suspected of HCC for their AFP level and they were further screened through LFTs. The findings of our study showed a higher frequency of the pathological levels of AFP in men as compared to women. This is consistent with the findings of previous studies which reported higher AFP concentration for males as compared to females [20]. Previous studies also reported an elevated AFP level that corresponds to HCC or HBV as an important marker for HCC diagnosis [21, 22, 23]. In our study, we found that AFP level for older individuals (>60) was comparatively higher for both genders as compared to younger individuals. Previous studies also reported a significant increase in serum AFP level for both men and women with the increase

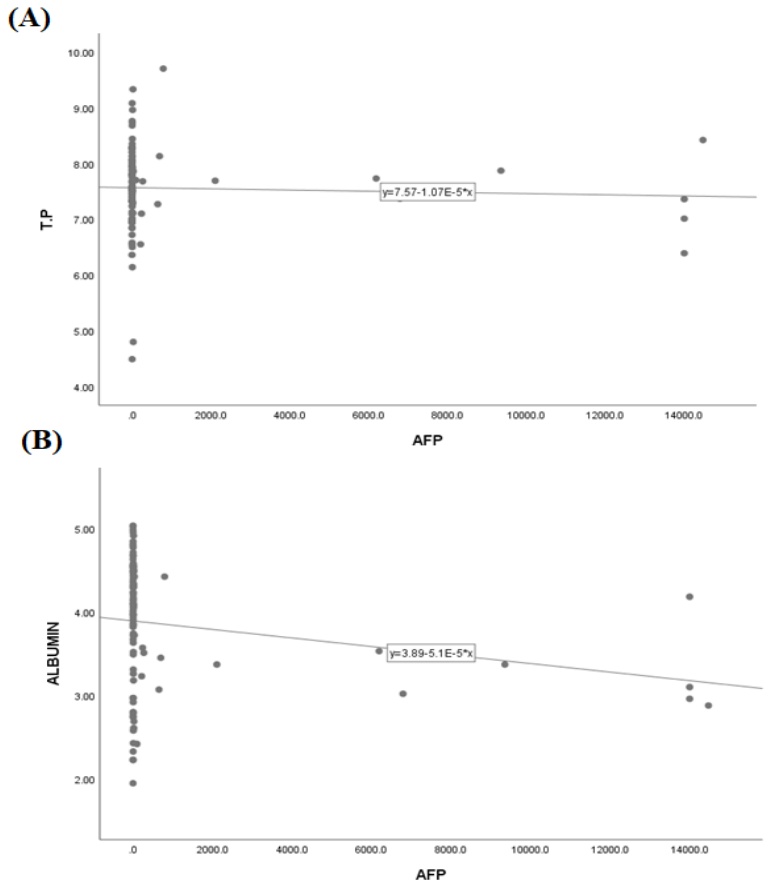

Figure 4. The graph shows Pearson correlation between (A) alpha-fetoprotein and total protein. AFP is shown on x-axis and T.P. on y-axis. There is no significant (p= 0.76) correlation between AFP and ALT (r2= 0.002). (B) alpha-fetoprotein and albumin. X-axis shows AFP and Y-axis shows albumin. There is no significant correlation between AFP and albumin (p= 0.07, r2= 0.041). P < 0.05 is considered as significant for each association

in age, stating age as an important determinant of AFP level [20, 23, 24]. However, among females of age group 20-40, no case of pathological levels of AFP was recorded. This might be a result of sampling bias or it may confirm the low frequency of high AFP level in younger females as reported earlier. We found no significant association between AFP and ALT, T.P. and/or albumin. A previous study reported disproportionality between the levels of AFP and ALT in case of HCC. However, it correlates positively only in cases of HCV. It was also reported previously that an increase in AFP level without a parallel increase in ALT could predict HCC with high specificity [17, 25, 26]. Our study found a significant association between AFP and AST levels (p= 0.021, r^2= 0.15). A similar finding was

reported by Tsai *et a*l, in which serum AST was positively correlated with serum AFP (r = 0.201, P = 0.007) [26]. Serum AST concentration reportedly influences the concentration of AFP in patients of HCV with liver cirrhosis in HCC diagnosis. The results of conventional LFTs for patients with high AFP serum level were worse than for those with a normal AFP value [27]. It shows that while interpreting the level of association between AST and AFP in cases of HCC, we must consider other pathological liver conditions and the history of patient that might influence the interpretation of algorithms.

5. Conclusion

We conclude from this study that the frequency of the pathological levels of tumor biomarker AFP among suspected HCC patients is higher in males as compared to females and also in older age groups. AFP levels are significantly relatable to AST levels but not relatable to ALT and albumin levels. For better interpretation of AFP based diagnosis and predictions, the correlation between LFTs and AFP level should be assessed keeping in view other liver conditions that may affect its level.

References

[1] Sherman M. Hepatocellular carcinoma: epidemiology, surveillance, and diagnosis. *Semin Liver Dis*. 2010; 30(1): 3–10. doi: 10.1055/s-0030-1247128

[2] Malaguarnera G, Giordano M, Paladina I, Berretta M, Cappellani A, Malaquarnera M. Serum markers of hepatocellular carcinoma. *Dig Dis Sci*. 2010;55(10): 2744–2755.

[3] Burtis CA, Ashwood ER (Eds.). *Tietz textbook of clinical chemistry*. Philadelphia, PA: WB Saunders; 1998.

[4] Chen Y, Zhao Y, Feng L, Zhang J, Zhang J, Feng G. Association between alpha-fetoprotein and metabolic syndrome in a Chinese asymptomatic population: a cross-sectional study. *Lipids Health Dis*. 2016;15(1): 85.

[5] Chen DS, Sung JL. *Serum alphafetoprotein in hepatocellular carcinoma. Cancer*. 1977;40(2): 779–783.

[6] Nomura F, Ohnishi K, Tanabe Y. Clinical features and prognosis of hepatocellular carcinoma with reference to serum alpha-fetoprotein levels: analysis of 606 patients. *Cancer*. 1989;64(8): 1700–1707.

[7] Li MS, Li PF, Yang FY, He SP, Du GG, Li G. The intracellular mechanism of alpha-fetoprotein promoting the proliferation of NIH 3T3 cells. Cell Res. 2002; 12(2): 151.

[8] Forner A, Bruix J. Biomarkers for early diagnosis of hepatocellular carcinoma. Lancet Oncol. 2012;13(8): 750–751.

[9] Peng S-Y, Chen WJ, Lai PL, Jeng YM, Sheu JC, Hsu HC. High α-fetoprotein level correlates with high stage, early recurrence and poor prognosis of hepatocellular carcinoma: Significance of hepatitis virus infection, age, p53 and β-catenin mutations. *Int J Cancer*. 2004;112(1): 44–50.

[10] Volk ML, Hernandez JC, Su GL, Lok AS, Marrero JA. Risk factors for hepatocellular carcinoma may impair the performance of biomarkers: a comparison of AFP,

DCP, and AFP-L3 1. *Cancer Biomark*. 2007;3(2): 79–87.

[11] Tateyama M, Yatsuhashi H, Taura N, Motoyoshi Y, Nagaoka S,… Ishibashi H. Alpha-fetoprotein above normal levels as a risk factor for the development of hepatocellular carcinoma in patients infected with hepatitis C virus. *J Gastroenterol.* 2011;46(1): 92–100.

[12] Heyward WL, Bender TR, Lanier AP, Francis DP, McMahon BJ, Maynard JE. Serological markers of hepatitis B virus and alpha-fetoprotein levels preceding primary hepatocellular carcinoma in alaskan eskimos. *The Lancet*. 1982;320(8304): 889–891.

[13] Purkins L, Love ER, Eve MD, Wooldridge CL, Cowan C,...Rapeport WG. The influence of diet upon liver function tests and serum lipids in healthy male volunteers resident in a Phase I unit. *Br J Clin Pharmacol*. 2004;57(2): 199–208.

[14] Sultana C, Dita C, Botescu A, Grancea C, Ruta S. Serum alpha fetoprotein, a surrogate marker for liver disease progression in chronic hepatitis C. *Roum Arch Microbiol Immunol*. 2014;73(3-4): 69–73.

[15] Tai W-C, Hu, T-H, Wang J-H, Hung C-H, Lu S-N, ... Chien C-M. Clinical implications of alpha-fetoprotein in chronic hepatitis C. *J Formosan Med Assoc*. 2009;108(3): 210–218.

[16] Hyder MA, Hasan M, Mohieldein AH. Comparative levels of ALT, AST, ALP and GGT in liver associated diseases. *Eur J Exp Biol.* 2013;3(2): 280–284.

[17] Richardson P, Duan Z, Kramer J, Davila JA, Tyson GL, El-serag HB. Determinants of serum alpha-fetoprotein levels in hepatitis C–infected patients. *Clin Gastroenterol Hepatol.* 2012;10(4): 428–433.

[18] Limdi J, Hyde G. Evaluation of abnormal liver function tests. *Postgrad Med J*. 2003;79(932): 307–312.

[19] El-Serag HB, Kanwal F, Davila JA, Kramer J, Richarddon P. A new laboratory-based algorithm to predict development of hepatocellular carcinoma in patients with hepatitis C and cirrhosis. *Gastroenterology*. 2014;146(5): 1249–1255.

[20] Ball D, Rose E, Alpert E. Alpha-fetoprotein levels in normal adults. *Am J Med Sci.* 1992;303(3): 157–159.

[21] Moore SW, Millar AJ, Hadley GP, Lonescu G, Kruger M,…Wessels G. Hepatocellular carcinoma and liver tumors in South African children. *Cancer*. 2004;101(3): 642–649.

[22] Baig JA, Alam JM, Mahmood SR, Baig M, Shaheen R,… Abdul Waheed. Hepatocellular carcinoma (HCC) and diagnostic significance of A-fetoprotein (AFP). *J Ayub Med Coll*. 2009;21(1): 72–75.

[23] Bruden DL, McMahon BJ, Hennessy Tw, Christensen CJ, Homan CE,… Bulkow LR. Estimating the date of hepatitis C virus infection from patient interviews and antibody tests on stored sera. *Am J Gastroenterol.* 2004;99(8): 1517.

[24] Vogel CL, Primack A, Mclntire KR, Carbone PP, Anthony PP. Serum

alpha-fetoprotein in 184 ugandan patients with hepatocellular carcinoma: *clinical, laboratory, and histopathologic correlations. Cancer*. 1974;33(4): 959–964.

[25] Chung TW, Kim JR, Suh JI, Lee YC, Chang YC,... Kim CH. Correlation between plasma levels of matrix metalloproteinase (MMP)-9/MMP-2 ratio and α-fetoproteins in chronic hepatitis carrying hepatitis B virus. *J Gastroenterol Hepatol.* 2004;19(5): 565–571.

[26] Tsai JF, Chang WY, Jeng JE, Ho MS, Lin ZY, Tsai JH. Frequency of raised α-fetoprotein level among Chinese patients with hepatocellular carcinoma related to hepatitis B and C. *Br J Cancer*. 1994;69(6): 1157–1159.

[27] Kim KA, Lee JS, Jung ES, Kim JY, Bae WK,… Moon YS. Usefulness of serum alpha-fetoprotein (AFP) as a marker for hepatocellular carcinoma (HCC) in hepatitis C virus related cirrhosis: analysis of the factors influencing AFP elevation without HCC development. *Korean J Gastroenterol.* 2006;48(5): 321–326.