

Assessment of KL-6 as a tumor marker in patients with hepatocellular carcinoma

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Received: 2005-03-13

Accepted: 2005-04-30

improved specificity of AFP for HCC diagnosis from 78% for AFP alone; 93% for AFP plus PIVKA-II to 99% for both plus KL-6 value ($P < 0.001$). Mean serum alkaline phosphatase level was significantly higher in KL-6 positive (564 ± 475) in comparison with KL-6 negative (505 ± 469) HCC patients ($P = 0.021$), but such a difference was not found among non-HCC corresponding groups.

CONCLUSION: KL-6 is suggested as a tumor for HCC. Its positivity may reflect HCC-associated cholestasis and/or local tumor invasion.

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Key words: Tumor markers; Liver disease; Hepatocellular carcinoma

Gad A, Tanaka E, Matsumoto A, Wahab MA, Serwah AeH, Attia F, Ali K, Hassouba H, el-Deeb AeR, Ichijyo T, Umemura T, Muto H, Yoshizawa K, Kiyosawa K. Assessment of KL-6 as a tumor marker in patients with hepatocellular carcinoma. *World J Gastroenterol* 2005; 11(42): 6607-6612
<http://www.wjgnet.com/1007-9327/11/6607.asp>

Abstract

AIM: To investigate the clinical significance of KL-6 as a tumor marker of HCC in two different ethnic groups with chronic liver disease consecutively encountered at outpatient clinics.

METHODS: Serum KL-6 was measured by the sandwich enzyme immunoassay method using the KL-6 antibody (Ab) as both the capture and tracer Ab according to the manufacturer's instructions (Eisai, Tokyo, Japan). Assessment of alpha fetoprotein (AFP) and protein induced vitamin K deficiency or absence (PIVKA-II) was performed in both groups using commercially available kits.

RESULTS: A significantly higher mean serum KL-6 (556 ± 467 U/L) was found in HCC in comparison with non-HCC groups either with (391 ± 176 U/L; $P < 0.001$) or without (361 ± 161 U/L; $P < 0.001$) liver cirrhosis (LC). Serum KL-6 level did not correlate with either AFP or PIVKA-II serU/Levels. Using receiver operating curve analysis for KL-6 as a predictor for HCC showed that the area under the curve was 0.574 (95%CI = 0.50-0.64) and the KL-6 level that gave the best sensitivity (61%) was found to be 334 U/L but according to the manufacturer's instructions; a cut-off point of 500 U/L was used that showed the highest specificity (80%) in comparison with AFP and PIVKA-II (78% vs 72% respectively). Combining the values of the three markers

INTRODUCTION

Hepatocellular carcinoma (HCC) is the 4th most common cancer worldwide, and it is a well-known complication of chronic hepatitis^[1,2]. Asymptomatic patients diagnosed as HCC through screening programs are more likely to be candidates for curative treatment and have improved short- and medium-term survival^[3,4]. Although serum alpha-fetoprotein (AFP) had been shown to be associated with HCC since 1963^[5], unfortunately it is also elevated in a wide variety of non-hepatic malignancies^[6,7] and benign hepatic conditions^[8,9]. Moreover, it is uncertain whether serum AFP is a useful marker for HCV-related HCC in some ethnic groups e.g., North American patients of African origin^[10]. Thus, searching another tumor marker, that together with AFP could improve the diagnostic utility of the later, seemed to be justified. KL-6 was originally found using a murine monoclonal antibody that recognized an undefined sialylated carbohydrate chain on a mucin-like glycoprotein^[11] which was also defined as MUC1^[12]. The cell membrane MUC1 was found to regulate cell adhesion properties^[13]. KL-6 has been first shown to be

Table 1 Background data of the study groups

	Egyptian		P	Japanese		P
	HCC (+) n = 65	HCC (-) n = 106		HCC (+) n = 45	HCC (-) n = 128	
Mean age (SD, yr)	57±11 ^b	47±9	<0.001	66±10 ^b	63±10	NS
Age <50 yr	16 (25) ^d	65 (61)	<0.001	3 (7) ^d	17 (13)	NS
Male	50 (77)	82 (77)	NS	38 (84)	87 (68)	0.024
Liver disease						
Viral	61 (94)	96 (91)		44 (98)	107 (84)	
HCV-related	59 (91)	92 (87)	NS	36 (80)	81 (63)	0.031
HBV-related	2 (3) ⁱ	4 (4)	NS	8 (18) ⁱ	28 (22)	NS
Non-viral	4 (6)	10 (9)	NS	1 (2)	20 (16)	0.010
Cirrhosis	46 (71)	45 (42)	<0.001	40 (89)	40 (31)	<0.001
Child's C	25 (38) ^f	17 (16)	0.001	4 (9) ^f	1 (1)	0.017
Mean±(SD)						
ALT (IU/L)	73±95	66±45	0.08	55±35	50±39	NS
Serum Albumin (g/L)	3.0±0.7	3.0±0.5	NS	3.6±0.5	4.2±0.4	<0.001
Platelet count×1 000/mL ³	186±107 ^h	89±53	0.001	130±51 ^h	170±71	<0.001
AFP >10 ng/mL (+)	64 (99)	28 (26)	<0.001	30 (67)	23 (18)	<0.001
PIVKA>40 mAU/L (+)	51 (79)	38 (36)	<0.001	16 (36)	27 (21)	0.047

^bP<0.001, ^dP<0.001, ⁱP<0.001, ^hP<0.001 vs Japanese, ^fP = 0.001.

elevated in patients with interstitial pneumonia^[14]. It was also reported to have a high positive rate in different non-hepatic malignancies and its expression was also correlated with metastatic potential of the primary tumor in some of them^[15-17]. It has also been studied as a fibrosis marker in patients with HCV-related chronic liver disease^[18] and was found to correlate with the degree of irregular regeneration of hepatocytes^[19]. A recent study addressed its clinical significance as a tumor marker in HCV-related HCC^[20]. However, all these studies investigated KL-6 in HCV-related disease only so that its actual significance as a marker for screening HCC in patients with different chronic liver disease is not yet fully understood. In this study, we aimed to investigate KL-6 as a tumor marker in consecutive patients with chronic liver disease seen at outpatient settings in two different ethnic groups of possible different risk factors for HCC, so that we could get a wider spectrum of disease in order to assess KL-6 validity for HCC screening.

MATERIALS AND METHODS

Study population

We conducted a cross-sectional study between October 2001 and November 2002. Data were gathered from two Affiliations; Shinshu University (Japan) and Suez Canal University (Egypt) Hospitals. A total of 334 consecutive patients with chronic liver disease seen at outpatient liver clinics in the two settings (who met our inclusion/exclusion criteria) were included; of them: 110 patients were diagnosed as HCC with a mean age of 61±11 years and M:F (4:1). Sixty-five were Egyptians and 45 Japanese with viral-related liver disease accounting for 94% and 98% of them respectively. Non-HCC patients were 234 with a mean age of 56±13 years; M:F (7/3). One hundred and six were Egyptians and 128 Japanese with viral-related liver disease accounting for 91% and 84% of them respectively

(Table 1).

Chronic liver disease and cirrhosis were identified and diagnosed according to liver biopsy findings, clinical and/or radiological evidence of portal hypertension. HCC was excluded by imaging studies (abdominal ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI) and/or hepatic angiography), one of which must have been performed at least 6 months following the measurement of AFP.

HCC was diagnosed when meeting our inclusion criteria of positive cytology and/or histology or by the presence of characteristic hepatic masses on liver CT, MRI and/or hepatic angiography (i.e., enlarging tumors and/or tumors with typical arterial vascularization).

We excluded patients with alcoholic and schistosomal liver diseases from our study populations. We had also excluded patients known from their medical history to have interstitial lung fibrosis or any other lung disease from our study population.

Tumor markers measurement

Serum KL-6 was measured by the sandwich enzyme immunoassay method using the KL-6 antibody (Ab) as both the capture and tracer Ab (14) according to the manufacturer's instructions (Eisai, Tokyo, Japan). KL-6 cut-off point was set at 500 U/L for this study. Assessment of alpha fetoprotein (AFP) and protein-induced vitamin K deficiency or absence (PIVKA-II) was performed using commercially available kits. Cut-off points were set at 10 ng/mL for AFP and 40 mAU/L for PIVKA-II.

Statistical analysis

Univariate statistical analysis was performed using Student's *t*-test for quantitative and χ^2 test with Yates' correction for qualitative data. Fisher's exact test was used

for comparison of small numbers; statistical significant level was set at $P < 0.05$. Statistical analysis was performed using a computer software (SPSS, version 6.0).

RESULTS

Population background

A difference in mean age, prevalence of advanced Child class and HBV infection was observed between Egyptian and Japanese patients with HCC (Table 1). However, no difference in tumor characteristics was found between the two studied populations (Table 2).

KL-6 and other tumor markers in HCC

A significantly higher mean serum KL-6 (556 ± 467) was found in HCC in comparison with non-HCC groups of patients with (391 ± 176 ; $P < 0.001$) and without (361 ± 161 ; $P < 0.001$) liver cirrhosis (LC). Serum KL-6 level did not correlate with either AFP (Figure 1) or PIVKA-II (Figure 1) serU/Levels. Using receiver operation characteristic (ROC) curve, the KL-6 level that gave the best sensitivity (61%) was found to be 334 U/L with a specificity of 50%, while PIVKA-II and AFP showed a sensitivity/specificity of (60/72)% and (80/78)% respectively. However, according to the manufacturer's instructions; a cut-off point of 500 U/L was used in this study that showed the highest

Table 2 Comparison of background tumor characteristics between Egyptian and Japanese HCC patients

Tumor characteristic	Egyptian (n = 65)	Japanese (n = 45)	P
Tumor multiplicity			
Solitary	25 (38)	22 (49)	>0.2
Multiple	40 (62)	23 (51)	0.06
Tumor size			
<3 cm	32 (49)	20 (44)	>0.2
3:<5cm	15 (23)	14 (31)	>0.2
≥5 cm	18 (28)	11 (25)	0.13
Metastases	01 (2)	>0.2	
Tumor grade ¹			
Well differentiated	5 (16)	2 (8)	>0.2
Poorly differentiated	5 (16)	4 (16)	>0.2

¹Tumor grade is analyzed in 32 of the Egyptian and 22 of the Japanese groups who passed HCC resection operation during the study period.

specificity (80%) for KL-6 in comparison with the other two markers. Combining the values of KL-6; AFP and PIVKA-II resulted in improvement in the specificity of AFP for HCC diagnosis from 78% for AFP alone; 93% for AFP plus PIVKA-II to 99% for both plus KL-6 ($P < 0.001$) (Table 3).

Factors associated with positive KL-6 in the study population

Univariate analysis (Table 4) of possible factors that

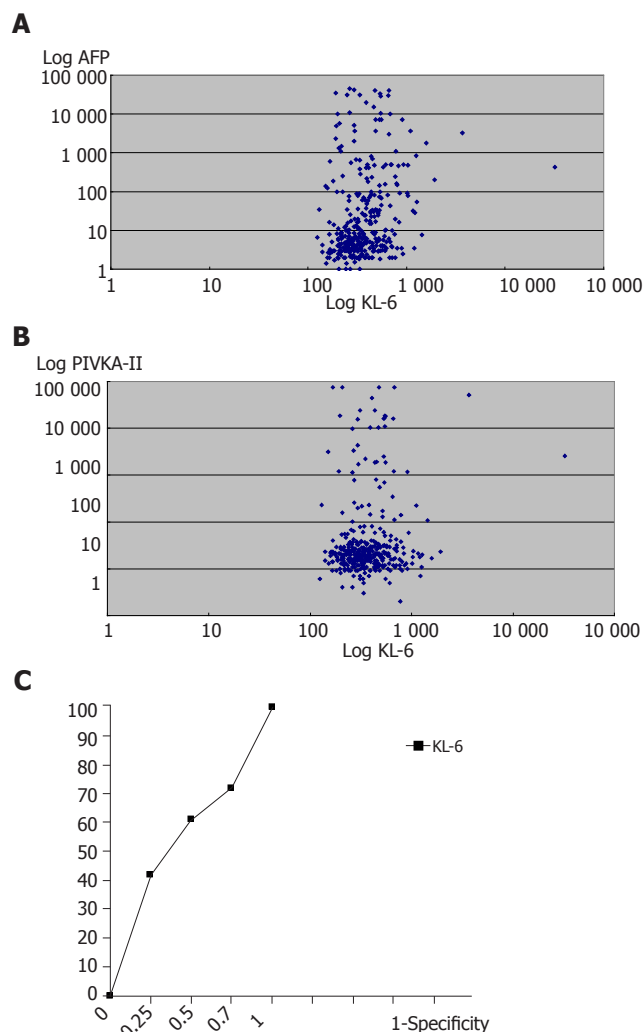


Figure 1 A: Correlation between KL-6 U/L and AFP ng/ml serU/Levels in the study population. $C = 0.04$, $P > 0.1$. The Log values of both markers are shown; **B:** Correlation between KL-6 U/L and PIVKA-II mAU/L serU/Levels in the study population. $C = 0.03$, $P > 0.5$. The Log values of both markers are shown; **C:** Receiver operating characteristic curves for KL-6 as predictors of HCC. The area under the ROC was found to be 0.574 (95%CI = 0.50–0.64). The best KL-6 sensitivity was obtained at a cut-off point = 334 U/L.

could be associated with elevated serum KL-6 in our study group showed that elevated AFP ($P < 0.001$), Child's class C ($P = 0.002$), Egyptian race ($P = 0.003$) and HCC ($P = 0.008$) were significantly associated with positive serum KL-6. Also mean serum alkaline phosphatase level was significantly higher in KL-6 positive (564 ± 475) in comparison with KL-6 negative (505 ± 469) HCC patients ($P = 0.021$), but such a difference was not found among non-HCC corresponding group (Table 5). Mean serum bilirubin was found to be higher in KL-6 positive subgroups in both HCC and non-HCC ($P = 0.077$, 0.023) respectively, while mean serum albumin was significantly lower in both groups ($P = 0.029$, 0.041), respectively (Table 5).

KL-6 in Egyptian vs Japanese

Mean KL-6 was significantly higher in Egyptians (576 ± 522) in comparison with Japanese (510 ± 300) HCC

Table 3 Comparison of the result of different tumor markers between HCC and non-HCC group

Tumor marker (cut-off point)	Sensitivity	Specificity
	%	%
AFP (10 ng/mL)	86	78
PIVKA-II (35 mAU/L)	61	72
KL-6 (500 U/L)	34	80
AFP+PIVKA-II	86 ¹	93
AFP+KL-6	87 ²	94
AFP+PIVKA-II+KL-6	87	99

¹All PIVKA-II (+) HCC patients are AFP (+). ²One KL-6 (+) HCC patient is AFP (-).

Table 4 Factors associated with KL-6 positivity in the study population

Factors	Total	KL-6 (+)	KL-6 (-)
Age (yr)			
>=50	244	60 (24)	184 (75)
<50	100	24(24)	76 (76)
<i>P</i>	NS		
Sex			
Male	257	61 (24)	196 (76)
Female	87	23 (26)	64 (73)
<i>P</i>	NS		
Ethnicity			
Egyptian	171	53 (31)	118 (69)
Japanese	173	31 (18)	142 (82)
<i>P</i>	0.003		
Underlying liver disease			
HCV-related	267	71 (27)	196 (73)
HBV-related	42	5 (12)	37 (88)
Non-viral	35	8 (23)	27 (77)
<i>P</i>	NS		
Cirrhosis			
(+)	169	46 (27)	123 (73)
(-)	175	38 (22)	137 (78)
<i>P</i>	NS		
Child's class			
C	47	20 (43)	27 (57)
A&B	297	64 (21)	233 (78)
<i>P</i>	0.002		
HCC:			
(+)	110	37 (34)	73 (66)
(-)	234	47 (20)	187 (80)
<i>P</i>	0.008		
AFP			
(+)	145	49 (34)	96 (66)
(-)	199	35 (17)	164 (82)
<i>P</i>	<0.001		

patients ($P = 0.041$) (Table 6). Although a significant difference in mean KL-6 level between HCC and non-HCC was observed in both Egyptian and Japanese patients with chronic liver disease ($P < 0.001$ respectively), the difference was not statistically significant among Japanese patients with HCV-related disease (Table 6). No difference in mean KL-6 level was found between cirrhotic and non-cirrhotic in either HCC or non-HCC patients.

KL-6 and tumor characteristics

In the HCC groups of both Egyptian and Japanese patients; KL-6 showed no significant association with tumor site, echogenicity or multiplicity. However, a significantly lower mean KL-6 (Table 7) was noticed in larger size tumors of >5 cm (371 ± 168 U/L) in comparison with tumors of less than or equal to 5 cm (537 ± 323) ($P < 0.05$ in the Japanese group).

DISCUSSION

KL-6 was studied as a tumor marker in different malignancies like breast, lung and pancreatic cancer and it was reported to be elevated in up to 50% of these malignancies^[14]. Two previous studies by Moriyama *et al*^[19, 20] addressed KL-6 as a tumor marker for HCC in patients with HCV-related chronic liver disease, and his results showed that the estimated cumulative incidence of HCC development in HCV-related chronic liver disease patients was significantly greater in patients with positive KL-6^[19] and suggested KL-6 to be used as a serological marker for HCC development in HCV-positive patients^[20]. In our study, we included consecutive patients with chronic liver disease seen at outpatient settings in two different ethnic groups of possible different risk factors for HCC^[22, 23] in order to have a wider spectrum of disease to judge KL-6 validity as a diagnostic test for HCC; however, one limitation was that most of the encountered patients in the two settings were actually with HCV-related disease with low proportion of HBV and non-viral-related disease. Our results showed a significantly higher mean KL-6 in HCC compared with non-HCC; either with or without LC; in addition no difference in mean KL-6 was found among HCC patients with and without LC; such findings together point to KL-6 association with HCC independent on the presence or absence of LC. A significantly higher mean KL-6 level was found in HBV-related in comparison with HCV-related HCC in both Egyptian and Japanese populations; a finding that deserves future study on a larger population of HBV-related disease. Our results also showed a significantly higher mean KL-6 level in HCC patients of Egyptian compared with Japanese race. The finding of a difference in the clinical background between both in terms of lower mean age and lower prevalence of HBV-related HCC could reflect a difference in the risk factors for HCC in both groups. Also, a higher prevalence of advanced Child class in the HCC Egyptian patients was observed that could stand behind the finding of higher mean KL-6 level in this group compared to their corresponding Japanese group. Although we excluded patients with overt schistosomal from this study, still some Egyptian patients had a past history of schistosomiasis with US evidence of hepatic periportal fibrosis (denoting a background of schistosomal liver disease) that could also explain the finding of higher mean KL-6 level in Egyptian HCC patients, if we consider the possibility that KL-6 could be a fibrosis marker too^[21]. This topic is highly suggested for future study.

Table 5 Comparison of the clinical profile of KL-6 positive and negative patients with and without HCC

	HCC (+)		P	HCC (-)		P
	KL-6 (+) n = 37	KL-6 (-) n = 73		KL-6 (+) n = 47	KL-6 (-) n = 187	
Mean age (yr) ¹	59±12	62±10	NS	57±12	56±13	NS
Cirrhosis	39 (81)	55 (76)	NS	16 (34)	65 (35)	NS
Child's C	13 (35)	15 (21)	NS	7 (15)	11 (6)	0.045
Mean ALT	74±101	62±61	NS	59±33	57±45	NS
Serum						
Albumin (g/L) ¹	2.9±0.7	3.3±0.7	0.029	3.5±0.9	3.8±0.8	0.041
Bilirubin (mmol/L) ¹	2.7±2.8	2.5±3.0	0.077	2.4±2.9	1.4±1.9	0.023
ALP (IU/L) ¹	564±475	505±469	0.021	316±139	299±152	NS
AFP (+)	36 (97)	58 (80)	0.013	13 (28)	37 (20)	NS
PIVKA (+)	23 (62)	44 (60)	NS	14 (30)	50 (27)	NS

¹Data is shown as mean±SD. Other data is shown as n (%).

Table 6 Comparison of mean serum KL-6 level among different study sub-groups

	Egyptian		P	Japanese		P
	HCC (+)	HCC (-)		HCC (+)	HCC (-)	
Chronic liver disease ¹ :	576 (522)	398 (185)	0.001	510 (300)	350 (147)	<0.001
HCV-related	558 (524)	400 (172)	0.008	356 (290)	382 (209)	>0.2
HBV-related	778 (663)	246 (72)	>0.2	877 (292)	340 (163)	<0.001
Non-viral	729 (538)	446 (309)	>0.2	262 ² ()	357 (160)	-
Cirrhotics	599 (586)	406 (159)	0.035	510 (350)	374 (196)	0.035
Non-cirrhotics	518 (325)	398 (185)	0.045	225 (73)	349 (222)	<0.001

¹The KL-6 values are shown as mean (SD) U/L. ²Only one patient's data.

Table 7 Difference in mean KL-6 level according to HCC size

	Egyptian (n = 65)	P ¹ value	Japanese (n = 45)	P value
Tumor size				
<3 cm	485±227		618±361	
3:<5 cm	643±685	>0.1	456±285	0.17
≥5 cm	581±420	>0.1	371±168	0.04

¹P value is shown for the difference group (<3 cm) and the other two groups.

We used a cut-off point of 500 U/L for KL-6 positivity in this study; however, applying the ROC analysis showed that a cut-off point of 334 U/L would give the best sensitivity in our study population of 60% compared with only 32% for a cut-off (500 U/L); however, the best specificity was obtained using the later. Moriyama *et al.*^{19,20]} used a cut-off point of 300 U/L in his analysis of KL-6 in HCV-related disease. KL-6 serU/Level did not correlate with either serum AFP or PIVKA-II levels, which points to its behavior independently from either of them and this may justify its clinical significance as an independent tumor marker for HCC diagnosis when considered with both AFP and PIVKA-II. Our results also supported this finding as AFP specificity for HCC diagnosis improved from 78% for AFP alone and 93% of both AFP and PIVKA-II to 99% when combined with KL-6. Univariate analysis showed that low serum albumin, hyperbilirubinemia and elevated ALP were significantly

associated with positive KL-6 in HCC patients, while KL-6 showed no association with LC in turn, and this denotes a possible association between positive KL-6 and deterioration of hepatic condition in HCC patients independent from their cirrhotic status; a finding that might point to KL-6 as a predictor of tumor aggression and/or local or systemic metastasizing potential. A follow-up study is needed to confirm its exact role in this regard.

ACKNOWLEDGMENTS

We would like to thank Takeda Foundation, Osaka, Japan for their financial support. We also thank Dr. Alla Sad, Dr. Essam Abd Alla, Dr. Khaled Gad for their help with various laboratory techniques.

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Science Editor Guo SY Language Editor Elsevier HK