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Original Article

The change of sICAM-1 and PIVKA-II after treatment of hepatocellular carcinoma as a predictor of patient survival

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Abstract: Objective: This study aimed to investigate the relationship between the change of sICAM-1 and PIVKA-II after radical resection of hepatocellular carcinoma (HCC) and the prognosis of HCC. Method: Clinical data and prognosis of 137 patients who accepted radical resection of hepatocellular carcinoma were analyzed. Levels of sICAM-1 and PIVKA-II before and 1 month after surgery were examined. All the patients were divided into different groups according to the change of tumor makers after surgery. Survival rates were analyzed statistically between different groups. Result: Patients with sICAM-1 or PIVKA-II over the cutoff level had higher stage of TNM classification and Child-Pugh, higher rates of recurrence and worse survival. Patients with both sICAM-1 and PIVKA-II below the cut off level had the best survival. Conclusion: For the patients who accepted radical resection of HCC, combined analysis on the change of sICAM-1 and PIVKA-II may help to predict the prognosis of HCC.

Keywords: Hepatocellular carcinoma, sICAM-1, PIVKA-II, survival analysis

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignant carcinoma in the world [1]. With the development of treatment modalities, the prognosis of HCC patients is getting better. But the mortality of HCC still ranks the second in the world [2, 3]. Some tumor makers, such as AFP, AFP L3, ICAM-1 and PIVKA-II, have been used in the early diagnosis of HCC. However, the up-regulation of some tumor makers (such as AFP and AFP L3) can also be observed in patients with chronic hepatitis or liver cirrhosis [4, 5]. Soluble cell adhesion molecule-1 (sICAM-1) is positive in liver cancer tissue, but negative or weak positive in chronic liver disease, which is an accurate maker in the diagnosis of HCC [6]. Protein induced by vitamin K absence or antagonist II (PIVKA-II) has been regarded as one of the specific makers, which has been also used in the diagnosis of HCC [7].

In the past, the studies on the use of tumor makers focused on the diagnosis of HCC. So the level of tumor makers was usually examined before hepatectomy. There were not many studies on levels of the tumor makers after treatment. To study the change of tumor makers, we need to examine levels of the tumor makers before and after surgery. Now, it is proved that the levels of sICAM-1 and PIVKA-II after hepatectomy can predict the survival of HCC patients [8, 9]. Moreover, analysis of the combined tumor makers is proposed to be a better way to evaluate the prognosis of HCC. It has been reported that combined analysis of AFP and PIVKA-II is a useful way to predict the recurrence and prognosis of HCC. Furthermore, our previous study has indicated that the level of AFP and sICAM-1 is also associated with the recurrence and prognosis of HCC. High levels of AFP and sICAM-1 predict poor prognosis and a high rate of recurrence [10]. However, whether levels of PIVKA-II and sICMA-1 are correlated with the recurrence and the prognosis of HCC is still unknown.

In this study, levels of sICMA-1 and PIVKA-II before and after hepatectomy were first exam-

Table 1. Expression of sICAM-1 and PIVKA-II before and after surgery

	Expression Before surgery	n
sICAM-1		
	<1000	56
	>1000	81
PIVKA-II		
	<40	64
	>40	73
	Expression After surgery	n
sICAM-1		
	<1000	80
	>1000	57
PIVKA-II		
	<40	94
	>40	43

ined, and then the relationship between the change of tumor makers and clinical parameters was analyzed. Survival of patients was also analyzed to find its correlation with the change of tumor makers. Finally, the change of sICMA-1 and PIVKA-II was taken into consideration together to find out whether their change could influence the prognosis of the HCC patients and find out the possibility of using the two tumor makers to evaluate the survival and prognosis of HCC patients.

Materials and methods

Patient demographics

Data of 173 HCC patients who accepted hepatectomy between Oct, 2008 and Dec, 2012 were collected. Surgery was performed in the Department of Hepatology, Xijing Hospital. All the patients were diagnosed as HCC at the Department of Pathology, Xijing Hospital. Biopsy was also used to confirm that there were no remnant tumor cells around the tumor tissue after surgery. The serum levels of sICAM-1 and PIVKA-II were measured before and 1-2 months after surgery. After that, the levels were examined every 3 months. Computed tomography (CT) of the liver was performed every 6 months after hepatectomy to find out tumor recurrence.

At least 12-month follow-up was made after hepatectomy. Medium follow-up period was 47.5 months (range, 12-84 months). The study protocol was approved by the Ethics committee of Xijing hospital.

Grouping

ForsICAM-1, patients were divided into 3 groups according to sICAM-1 levels after hepatectomy. the sICAM-1 level both before and after hepatectomy was lower than the cut off level, we defined as group N; the level of sICAM-1 was above the cut off line but returned to the normal range after hepatectomy, we defined group D; the level of sICAM-1 was increased after hepatectomy, or decreased but still above the cut off line, we defined group IU, According to this grouping method, 20 (14.6%) patients were divided into N group, 60 (43.8%) in D group and 57 (41.6%) in IU group.

For PIVKA-II, patients were also divided into 3 groups according to the change of PIVKA-II after hepatectomy in the same way as sICAM-1. The case number of N, D, IU groups were 51, 43 and 43, respectively.

Measurement of tumor makers

Four mL peripheral blood samples were taken from each patient before and after hepatectomy during two months. First the blood underwent centrifugation at 3000 rpm for 10 min, and the plasma was obtained. Eitest PIVKA-II ELISA kit and sICMA-1 kit were used to detect the level of the tumor makers. The cutoff level of sICAM-1 was 1000 μg/mL, and the cutoff level of PIVKA-II was 40 mAU/mL.

Statistical analysis

SPSS 19.0 (IBM, USA) software was used for statistical analyses. Chi-square and Fisher's exact test were used to analyze the differences in categorical data between groups. Continuous data were analyzed by Student's t test or Mann-Whitney test. Kaplan-Meier method was used to calculate the overall survival and disease-free survival, and the difference of survival between different groups was tested using Log-rank test. Multivariate analysis was performed by Cox's proportional hazards regression modeling. It was considered to be significant when a two-tailed *p* value was less than 0.05 [10].

Table 2. Relationship between changes of sICAM-1 after hepatectomy and clinicopathological parameters

	Group N	Group D	Group IU	*p* value
Age	52.7±11.6	55.3±10.1	53.3±9.9	0.323 (t=2.263)
Gender (Male/Female)	16/4	45/15	41/16	0.770 (χ^2=0.524)
HBV-Ag+ (n, %)	14, 70.0%	50, 83.3%	49, 86.0%	0.264 (χ^2=2.665)
HCV-Ag+ (n, %)	5, 25.0%	5, 8.3%	6, 10.5%	0.125 (χ^2=4.165)
Child-Pugh (A/B)	17/3	49/11	36/21*	0.036 (χ^2=6.634)
TNM classification (1/2/3/4)	14/4/1/1	17/31/10/2**	24/18/11/4	0.025 (χ^2=14.429)
Tumor size (<2/2-5/>5 cm)	15/4/1	11/31/18**	18/17/22**	<0.001 (χ^2=26.254)
Number of tumors (solitary/multiple)	48/12	31/18	32/13	0.141 (χ^2=3.917)
Tumor recurrence (N/Y)	10/10	16/44	7/50**	0.003 (χ^2=11.908)

*compared to D, P<0.05. **compared to N, P<0.05.

Table 3. Relationship between changes of PIVKA-II after hepatectomy and clinicopathological parameters

	Group N	Group D	Group IU	*p* value
Age	53.2±9.9	54.0±10.5	55.2±10.5	0.397 (t=1.847)
Gender (Male/Female)	37/14	32/11	33/10	0.898 (χ^2=0.216)
HBV-Ag+ (n, %)	42, 82.4%	32, 74.4%	39, 90.7%	0.139 (χ^2=3.994)
HCV-Ag+ (n, %)	7, 13.7%	4, 9.3%	5, 11.6%	0.801 (χ^2=0.443)
Child-Pugh (A/B)	44/7	32/11	26/17**	0.017 (χ^2=8.170)
TNM classification (1/2/3/4)	26/23/2/0	15/17/10/1	14/13/10/6**	0.002 (χ^2=21.042)
Tumor size (<2/2-5/>5 cm)	23/21/7	14/15/14	7/16/20**	0.005 (χ^2=14.818)
Number of tumors (solitary/multiple)	41/10	31/12	28/15	0.248 (χ^2=2.787)
Tumor recurrence (N/Y)	19/32	10/33	4/39**	0.007 (χ^2=9.993)

**compared to N, P<0.05.

Result

Characteristics of patients

11 of 173 (8.1%) patients lost follow-up, 1 patient who died of accident and 24 who died of unrelated disease were excluded from this study. 137 patients were finally included into statistical analyses. There were 102 males (74.5%) and 35 females (25.5%). The ratio of males/females was 2.91. Mean age of patients at hepatectomy was 54.1±10.2 years (range, 24-68 years). 113 patients were associated with hepatitis B virus (82.5%), and 16 patients associated with hepatitis C virus (11.7%). Liver function of all the patients was assessed by Child-Pugh classification and tumor node metastasis (TNM) classification. According to the Child-Pugh classification, 102 patients (74.5%) were classified as grade A and 35 classified as grade B (25.5%). Regarding to pathological TNM stage, there were 51 patients (37.2%) of stage I, 50 (36.5%) of stage II, 33 (24.1%) of stage III, and 3 (2.2%) of stage IV. For the level of sICAM-1, there were 56 patients below the cutoff line and 81 patients above the cutoff line before surgery. The numbers were 80 and 57 after surgery. 64 patients had a normal expression of PIVKA-II before surgery and 73 had an abnormal expression. The number changed to 94 and 43 after surgery (**Table 1**).

Clinicopathological parameters, serum levels of tumor markers and the change in sICAM-1

The relationship between the changes of sICAM-1 levels and various clinicopathological parameters was listed in **Table 2**. It was found that there was no significant difference between groups in age, gender, the infection of HBV/HCV and the number of tumor (Age: t=2.263, P=0.323; gender: χ^2=0.524, *P*=0.770; infection of HBV: χ^2=2.665, *P*=0.264; infection of HCV: χ^2=4.165, *P*=0.125; number of tumors: χ^2=3.917, *P*=0.141). However, significant differ-

ences between different groups were observed in the Child-Pugh classification, the TNM classification, tumor size and the number of patients with tumor recurrence. The IU group and D group had more tumor recurrence (50.0% in N group, 73.3% in D group, 87.7% in IU group, χ^2=11.908, *P*=0.003), and a higher percentage of Child-Pugh B liver function (15.8% in N group, 18.3% in D group, 36.8% in IU group, χ^2=6.634, *P*=0.036). Advanced TNM stage (χ^2=14.429, *P*=0.025) and lager tumor size (χ^2=26.254, *P*<0.001) were also associated with the incidence of IU group.

Clinicopathological parameters, serum levels of tumor markers and the change in PIVKA-II

Relationship between clinicopathological parameters and the change of PIVKA-II is listed in **Table 3**. Similar to sICAM-1, the D group and IU group of PIVKA-II also had more patients with Child-Pugh B liver function (χ^2=8.170, P=0.017), more tumor recurrence (χ^2=9.993, *P*=0.007), advanced TNM stage (χ^2=21.042, *P*=0.002) and lager tumor size (χ^2=14.818, *P*=0.005). Other clinicopathological parameters, including gender (χ^2=0.216, *P*=0.898), infection of HBV (χ^2=3.994, *P*=0.139), number of tumor (χ^2=2.787, *P*=0.248), age (t=1.847, P=0.397) and infection of HCV (χ^2=0.443, *P*=0.801), were not related to the change of PIVKA-II after hepatectomy.

Prognostic factors associated with tumor-free survival and overall survival

Different significant prognostic factors associated with the survival rate, including the disease-free survival rate and the overall survival rate, analyzed by univariate analysis and multivariate analysis, are listed in **Table 4**. In univariate analysis, absent tumor recurrence, Child-Pugh A liver function, elementary TNM classification, smaller tumor size, the N group and D group of sICAM-1, the N group and D group of PIVKA-II, and group A and B were significantly correlated with better disease-free survival. The same parameters also had better overall survival. Multivariate analysis revealed that tumor recurrence and advanced TNM stage were significantly correlated with poor disease-free survival and overall survival.

Discussion

How to evaluate the prognosis of HCC is always difficult in the treatment of HCC. Specific HCC makers, including AFP, PIVKA-II and sICAM-1, are commonly used in the prognosis evaluation and the diagnosis of HCC [7]. It has been proved that higher levels of these tumor makers are closely related with the development and recurrence of HCC [11]. In clinical practice, these makers have been used to reflect patient prognosis after treatment. It is reported that PIVKA-II and sICAM-1 have been used as independent prognostic markers for HCC patients who undergo hepatectomy.

It was found that ICAM-1 was negative in normal liver tissues but positive in over 80% of HCC patients. Moreover, the expression of ICAM-1 was very low in benign chronic liver disease, such as HBV, HCV and liver cirrhosis [8]. It was pointed out that the level of ICAM-1 was associated with malignant transformation of carcinoma [12]. It was also noticed that the increase of free form ICAM-1 in plasma-sICMA-1 was also found in HCC patients [13]. It was reported that the level of sICAM-1 was much higher in patients with higher stage of TNM [14].

PIVKA-II was also found to be associated with the development of HCC. It was proved that protein of PIVKA-II was highly expressed in hepatoma carcinoma cell line HepG2 and Hu7 and PIVKA-II was also able to promote proliferation of liver cancer cells [15, 16]. It was also found PIVKA-II played an important role in the ERK pathway [17, 18], which contributed to the proliferation and migration of vascular endothelial cells in HCC. PIVKA-II had long been used in the diagnosis of HCC. However, the upregulation of PIVKA-II was also found in patients with disregulated coagulation [18]. It may cause a false positive.

In this study, it was found that there was an opposite change of sICAM-1 and PIVKA-II in some patients. Using a single tumor maker to judge the prognosis of HCC was limited. In our previous study, a high preoperative level of sICAM-1 was associated with poor prognosis. In Nanashima's study [10], a high level of PIVKA-II was also associated with worse survival. In the present study, patients were divided into 3 groups according to the change of tumor makers. In our expection, patients of the N group showed the lowest malignancy before and after surgery, the D group may show an improvement after surgery and the IU group may have the most aggressive malignancy.

Table 4. Multivariate analysis by Cox's proportional hazard test of prognostic factors influencing tumor-free survival and overall survival in patients who underwent hepatectomy

Variable	Disease-free survival				Overall survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	RR[a] (95% CI)	*p* value	RR[a] (95% CI)	*p* value	RR[a] (95% CI)	*p* value	RR[a] (95% CI)	*p* value
Tumor recurrence								
No								
Yes	0.25 (0.16-0.39)	<0.001	0.19 (0.11-0.32)	<0.001	0.28 (0.19-0.43)	<0.001	0.27 (0.16-0.44)	<0.001
Child-Pugh classification								
A								
B	0.57 (0.39-0.85)	0.005	0.73 (0.45-1.17)	0.725	0.52 (0.35-0.77)	0.001	0.65 (0.41-1.03)	0.065
TNM classification								
1								
2	0.02 (0.01-0.07)	<0.01	0.02 (0.01-0.09)	<0.001	0.02 (0.01-0.09)	<0.001	0.04 (0.01-0.15)	<0.001
3	0.08 (0.02-0.28)	<0.01	0.14 (0.04-0.54)	0.004	0.09 (0.03-.030)	<0.001	0.17 (0.04-0.65)	0.010
4	0.27 (0.08-0.91)	0.035	0.39 (0.10-1.46)	0.162	0.36 (0.11-1020)	0.096	0.57 (0.15-2.71)	0.411
Tumor size								
<2 cm								
2-5 cm	0.42 (0.27-0.64)	<0.001	0.59 (0.34-1.01)	0.054	0.41 (0.26-0.63)	<0.001	0.61 (0.36-1.03)	0.063
>5 cm	0.70 (0.46-1.07)	0.097	0.61 (0.37-1.01)	0.054	0.70 (0.46-1.06)	0.088	0.65 (0.39-1.07)	0.087
Changes of sICAM-1								
N								
D	0.51 (0.30-0.85)	0.011	2.06 (0.88-4.82)	0.095	0.49 (0.29-0.82)	0.007	1.81 (0.78-4.18)	0.167
IU	0.77 (0.54-1.11)	0.162	1.32 (0.63-2.77)	0.465	0.67 (0.47-0.97)	0.032	0.97 (0.46-2.01)	0.927
Changes of PIVKA-II								
N								
D	0.59 (0.39-0.90)	0.013	1.43 (0.68-2.99)	0.348	0.65 (0.43-0.98)	0.040	1.49 (0.74-3.02)	0.265
IU	0.69 (0.45-1.06)	0.091	1.06 (0.53-1.01)	0.869	0.83 (0.54-1.27)	0.397	1.37 (0.69-2.71)	0.368
Combination of changes of sICAM-1 and PIVKA-II								
sICAM-1 N/D and PIVKA-II N/D								
sICAM-1 N/D and PIVKA-II IU*	0.46 (0.26-0.83)	0.009	0.821 (0.37-1.84)*	0.63	0.51 (0.28-0.91)	0.022	0.88 (0.39-1.96)*	0.746
sICAM-1 IU and PIVKA-II N/D	0.83 (0.44-1.57)	0.571			0.84 (0.45-1.59)	0.593		
sICAM IU and PIVKA-II IU	0.75 (0.41-1.36)	0.340			0.95 (0.52-1.71)	0.851		

[a]Risk Ratio, *Linear correlated covariate.

First, the relationship between clinicopathological parameters and different groups was analyzed, and the result showed that the sICAM-1 IU group and the PIVKA-II IU group were correlated with poor liver function and tumor recurrence. It meant that an upregulation or a high-level of sICAM-1 or PIVKA-II may be correlated with poor outcome of HCC. Thus the relationship between the disease-free/overall survival rate and different groups was investigated. It was indicated that the sICAM-1 N group showed significantly better survival than the D group or the IU group. However, the PIVKA-II N group showed better survival only in disease-free survival but not in overall survival. It meant that sICAM-1 may be a more valuable maker in evaluating the survival of HCC.

Then the change of both sICAM-1 and PIVKA-II was taken into consideration and the patients were into new groups. The N group and D group were classified into one group as these patients had a level below the cut-off line after surgery and their prognosis had no significant difference. In this way, the patients were divided into 4 groups. While multivariate analysis showed patients of the sICMA-1-ND/PIVKA-II-ND group had the best survival, in both disease-free and overall survival. However, there was no significant difference among the other 3 groups. The results showed that whatever it was sICMA-1 or PIVKA-II, the level over the cut-off line indicated poor prognosis. In the previous study, it was reported that a normal level of PIVKA-II was correlated with good prognosis [19]. Furthermore, the decrease of serum PIVKA-II within 2 weeks after hepatectomy may reflect a good prognosis but a higher PIVKA-II level may reflect poor survival [20]. Taking both the previous study and the present study into consideration, it was suggested that patients with a high level of PIVKA-II after hepatectomy should accept adjuvant therapy in order to prevent tumor recurrence and improve survival.

The combination of sICMA-1-IU and PIVKA-II-IU was the worst predictor of tumor-free and overall survival. In the Cox analysis, the PIVKA-II-ND/sICMA-1-ND group showed better prognosis and less recurrence. It was pointed out that patients of PIVKA-II-IU or sICAM-1-IU should be followed up carefully to find tumor recurrence as early as possible.

In summary, we conducted a retrospective analysis on prognosis of 137 HCC patients who received hepatectomy. Then the relationship between prognosis and the change of sICMA-1/PIVKA-II was analyzed. Compared to the change of PIVKA-II, a high level of sICMA-1 after surgery was significantly associated with better survival after hepatectomy based on multivariate analyses. Patients with a low level of both PIVKA-II and sICMA-1 showed the best survival after hepatectomy. The upregulation of either of the two tumor makers may indicate a poor prognosis. Careful follow-up and adjuvant chemotherapy were necessary for HCC patients who showed abnormal tumor makers at the early period after hepatectomy.

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Disclosure of conflict of interest

None.

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