

## Original Article

# Prognostic value of soluble MICA levels in the serum of patients with advanced hepatocellular carcinoma

Jian-Jun Li<sup>1,2,\*</sup>, Ke Pan<sup>1,2,\*</sup>, Mo-Fa Gu<sup>1,3,\*</sup>, Min-Shan Chen<sup>1,4</sup>, Jing-Jing Zhao<sup>1,2</sup>, Hui Wang<sup>1,2</sup>, Xiao-Ting Liang<sup>1,2</sup>, Jian-Cong Sun<sup>1,2</sup> and Jian-Chuan Xia<sup>1,2</sup>

## Abstract

Serum levels of soluble MHC class I-related chain A (sMICA) are related with the prognosis of various types of cancer; however, few studies on the prognostic value of sMICA in hepatocellular carcinoma (HCC) have been reported. In this study, we retrospectively investigated the relationship between sMICA levels and clinical features of advanced HCC, and we assessed the prognostic value of sMICA in advanced HCC. Furthermore, the relationship of serum sMICA levels and natural killer group 2, member D (NKG2D) expression on natural killer (NK) cells was also evaluated. We detected sMICA levels in the serum of 60 advanced HCC patients using enzyme-linked immunosorbent assay (ELISA) and measured expression levels of NKG2D on NK cells using flow cytometry. We found that serum sMICA levels in HCC patients were in the range of 0.10–6.21 ng/mL. Chi-square analyses showed that sMICA level was significantly related with only tumor size. Survival analysis showed that a high sMICA level was significantly related with poor prognosis among HCC patients. Multivariate analyses indicated that sMICA was an independent prognostic factor. In addition, the levels of CD56<sup>+</sup>NKG2D<sup>+</sup> NK cells were within the range of 11.2%–55.4%, and correlation analyses indicated that sMICA level was negatively correlated with the level of NKG2D<sup>+</sup> NK cells. Our results suggest that serum sMICA levels may be an independent prognostic factor for advanced HCC.

**Key words** Hepatocellular carcinoma, soluble MICA, prognosis

Hepatocellular carcinoma (HCC) is a common malignant carcinoma in the world, and the incidence is continuously rising. Moreover, this disease has a leading death rate among malignant carcinomas<sup>[1,2]</sup>. The most common treatment for HCC is surgical resection or transcatheter arterial chemoembolization (TACE)<sup>[3]</sup>. However, despite these treatment options, the prognosis of HCC remains poor because of a high incidence of

early postoperative recurrence and metastasis in the liver remnant. Indeed, the 5-year overall survival (OS) rate for patients with recurrent or metastatic HCC is less than 10%<sup>[4]</sup>. Therefore, searching the appropriate prognostic factors for HCC patients is critical for selecting post-operative treatment, TACE, or targeted therapy, and for prolonging patient survival.

Serum levels of marker proteins, including alpha-fetoprotein (AFP), des-γ-carboxy prothrombin (DCP), glypican-3 (GPC3), α-L-fucosidase (AFU), and transforming growth factor β1 (TGF-β), are commonly used to determine the prognosis of HCC<sup>[5]</sup>. However, relying on a single marker as a prognostic indicator for HCC patients causes considerable inaccuracy. To provide highly effective treatment, it is necessary to find more reliable serum markers in the immunological field for an accurate prognostic assessment.

The nonclassical major histocompatibility complex class I (MHC-I) molecule A (MICA) has a molecular structure similar to that of classical MHC-I molecules<sup>[6]</sup>.

**Authors' Affiliations:** <sup>1</sup>State Key Laboratory of Oncology in South China, Guangzhou, Guangdong 510060, P. R. China; <sup>2</sup>Department of Experimental Research, <sup>3</sup>Department of Radiation Oncology, <sup>4</sup>Department of Hepatobiliary Oncology, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong 510060, P. R. China.

\*Jian-Jun Li, Ke Pan, and Mo-Fa Gu contributed equally to this work.

**Corresponding Author:** Jian-Chuan Xia, State Key Laboratory of Oncology in South China, Department of Experimental Research, Sun Yat-sen University Cancer Center, 651 Dongfeng Road East, Guangzhou, Guangdong 510060, P. R. China. Tel: +86-20-87343173; Fax: +86-20-87343392; Email: xiajch@mail.sysu.edu.cn.

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MICA is a natural ligand for the activating receptor natural killer group 2, member D (NKG2D) expressed on the surface of natural killer (NK) cells. The binding of MICA to NKG2D triggers a cascade of signal transduction events that activates NK cells to release cytotoxic molecules and subsequently causes NK cells to identify and lyse target cells. Under physiologic conditions, MICA is only expressed in epithelial cells of the gastrointestinal tract and is only present at very low levels in most normal cells and tissues. However, many malignant carcinoma cells express high levels of MICA on their surface, making them susceptible to targeting and killing by NK cells<sup>[7]</sup>. Recent studies suggest that in addition to expressing membrane-bound MICA, carcinoma cells also have a mechanism to shed MICA from the cell surface into the extracellular domain, generating a soluble form (sMICA). This process leads to a decrease of membrane-bound MICA and an increase of sMICA. Experimental evidence confirms that upon binding to NKG2D, sMICA not only fails to activate NK cells but also further inhibits NK cell function via down-regulating the expression of NKG2D on the NK cell surface<sup>[8-10]</sup>. Therefore, a possible mechanism by which carcinoma cells escape immune surveillance is the expression and shedding of MICA as sMICA.

Previous studies have demonstrated that in some cancer types, such as ovarian cancer<sup>[11]</sup>, head and neck squamous cell carcinoma<sup>[12]</sup>, and multiple myeloma<sup>[13]</sup>, serum sMICA level is significantly related with patient prognosis. Indeed, a high level of sMICA is usually related with poor prognosis among cancer patients. Furthermore, sMICA can be used as an independent prognostic factor. However, sMICA and its prognostic value in hepatocellular carcinoma (HCC) are rarely studied. Therefore, we determined the serum level of sMICA in 60 patients with advanced HCC, evaluated its correlation with clinical parameters, analyzed its association with prognosis, and estimated the value of using serum sMICA level as a prognostic indicator for HCC patients. In addition, we examined the level of NKG2D-expressing NK cells in peripheral blood lymphocytes of HCC patients and analyzed its correlation with sMICA levels.

## Materials and Methods

### Specimens

Sixty patients (52 men and 8 women) with advanced HCC were enrolled at the Sun Yat-sen University Cancer Center and treated between December 2000 and May 2002. The median age was 40 years (range, 28–63 years). The study was approved by the Ethics Committee in this university. Informed consent was

obtained from each patient. All patients were hepatitis B surface antigen (HBsAg)-positive in serum. The diagnosis of HCC and TNM stage were determined according to the 6th edition of the standard of the Union for International Cancer Control, UICC2002<sup>[14,15]</sup>. The clinical diagnosis was based on several factors, including hepatitis B virus (HBV) infection, elevated serum AFP, imaging of liver space-occupying lesions, vascular and bile duct invasion, and hepatic or distant metastatic lesions. All 60 patients had stages III–IV disease and were not suitable for surgery; all underwent only TACE after primary diagnosis. Liver function was graded according to the Child-Pugh standard<sup>[16]</sup> as A, B, and C in 21, 22, and 17 patients, respectively. Serum and peripheral blood lymphocytes were collected from patients at the first treatment and stored in the tumor tissue bank of the Sun Yat-sen University Cancer Center. Patients were followed from the time of hospital admission until August 31, 2010.

### Measurement of sMICA in serum

Serum sMICA of HCC patients was measured using an ELISA kit (Ansell) according to the manufacturer's protocol. Briefly, after obtaining serum samples from these advanced HCC patients, standard serial dilutions and serum samples were added to each well in 96-well flat-bottom plates covering capture anti-MICA mAb. Detection anti-MICA mAb were added to the wells. HRP-conjugated anti-mouse Ab was added and color was developed using tetramethylbenzidine system. Absorbance values (at  $A_{450}$ ) by duplicate were plotted against dilutions and expressed as pg/mL.

### Flow cytometry

Peripheral blood lymphocytes were collected and stained using antibodies specifically designed for flow cytometry, including PE-Anti-NKG2D, APC-Anti-CD3, and FITC-Anti-CD56 (all from BD Bioscience Co.). The percentage of cells expressing surface receptor was determined by flow cytometer (FC500, Beckman Co.).

### Statistical analysis

The relationship between sMICA level and clinical parameters was determined using the Chi-square or Fisher's exact test. The relationship between sMICA level and prognosis was calculated by survival analysis and Cox multivariate regression analysis. The correlation between sMICA level and NKG2D level was evaluated by correlation analysis. The relationships between categorical variables were estimated by Chi-square test. Pearson correlation coefficients were calculated to estimate the correlations among continuous variables.

The Kaplan-Meier method was applied for survival analysis. The log-rank test was used to compare the survival rates among different groups. Statistical analyses were performed using SPSS 13.0 software. Two-tailed *P* values < 0.05 were considered significant.

## Results

### Association of serum sMICA levels with clinical characteristics of advanced HCC patients

ELISA showed that the serum sMICA level in the 60

HCC patients ranged from 0.10 to 6.37 ng/mL, with a median level of 0.95 ng/mL. sMICA level was related with tumor size, but not with age, gender, copies of HBV-DNA, number of tumors, serum AFP level, cirrhosis, or vascular invasion (Table 1).

### Relationship between serum sMICA levels and prognosis of advanced HCC patients

Sixty patients were divided into two groups by the median sMICA level of 0.95 ng/mL. In the group with the sMICA ≤ 1 ng/mL, 24 patients died and 8 survived. The

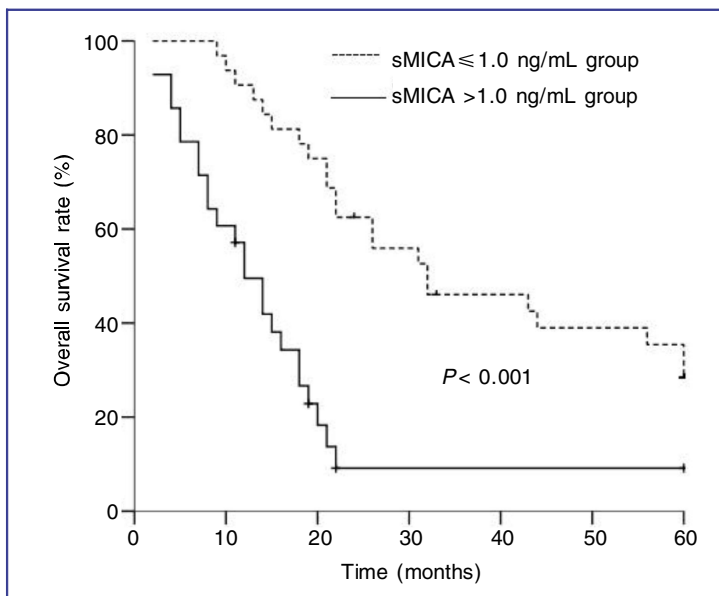
**Table 1. Relationship between serum sMICA levels and clinical features of patients with hepatocellular carcinoma (HCC)**

Clinicopathologic variable	Number of patients	sMICA level		<i>P</i>
		<1 ng/mL	≥ 1 ng/mL	
Total	60	32	28	
Gender				0.130
Male	52	30	22	
Female	8	2	6	
Age (years)				0.788
≤ 40	21	12	9	
> 40	39	20	19	
AFP (ng/mL)				0.069
< 25	31	20	11	
25–200	10	6	4	
> 200	19	6	13	
Serum HBV-DNA (copies)				0.796
≤ 10 <sup>3</sup>	32	18	14	
> 10 <sup>3</sup>	28	14	14	
Maximum diameter (cm)				0.001
≤ 5	22	18	4	
> 5	38	14	24	
Lymph node metastasis <sup>a</sup>				0.657
N0	55	30	25	
N1	5	2	3	
Hepatic or distant metastasis <sup>b</sup>				1.000
M0	53	28	25	
M1	7	4	3	
No. of lesions				0.208
1	31	14	17	
≥ 2	29	18	11	
Cirrhosis				0.259
Negative	18	12	6	
Positive	42	20	22	
Vascular invasion				0.454
Negative	52	29	23	
Positive	8	3	5	

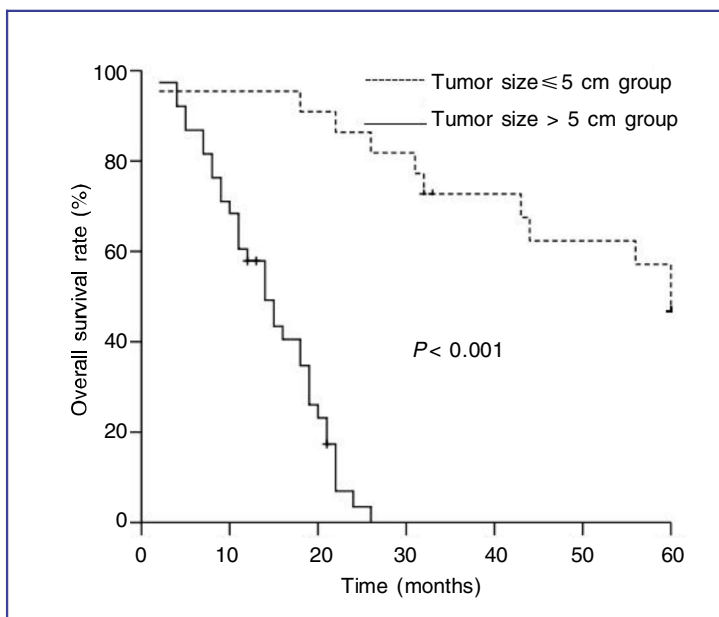
sMICA, major histocompatibility complex class I molecule A; AFP alpha-fetoprotein; HBV, hepatitis B virus. <sup>a</sup> or <sup>b</sup>, locoregional lymph node or hepatic/distant metastasis on computed tomography (CT) images.

mean survival time of 37.25 months, with a 95% confidence interval (CI) of 30.24–44.26 months. The median survival time was 32.0 months, with a 95% CI of 9.83–54.17 months. In the sMICA > 1 ng/mL group, 27 patients died and 1 survived. The mean survival time was 16.19 months, with a 95% CI of 10.26–22.12 months. The median survival time was 12.0 months, with a 95% CI of 8.32–15.68 months. Kaplan-Meier survival analysis revealed that patients with sMICA levels >1 ng/mL survived significantly shorter time than did those with sMICA levels ≤1 ng/mL (log-rank test,  $P < 0.001$ ) (Figure 1). Similar results were found when patients were divided into two groups based on tumor size. In the

group with tumor size ≤ 5 cm, the mean survival time was 47.67 months, with a 95% CI of 40.01–55.33 months. In the group with tumor size > 5 cm, the mean survival time was 14.30 months, with a 95% CI of 12.18–16.43 months. The Kaplan-Meier survival curves revealed that patients with tumor size >5 cm survived significantly shorter than did those with tumor size ≤5 cm ( $P < 0.001$ ) (Figure 2). The results suggest that higher sMICA level and larger tumor size in HCC patients were related with poor prognosis. In addition, when patients were divided into three groups (sMICA ≤ 1 ng/mL plus tumor size ≤ 5 cm; sMICA > 1 ng/mL plus tumor size > 5 cm; and other patients), a more



**Figure 1.** Kaplan-Meier survival curves of 60 advanced hepatocellular carcinoma (HCC) patients with different serum soluble major histocompatibility complex class I molecule A (sMICA) levels before transcatheter arterial chemo-embolization (TACE). Increased sMICA level is related with decreased patient survival rate. Patients in the high sMICA level group exhibited significantly poorer survival than did patients in the low sMICA level group (log-rank test,  $P < 0.001$ ).



**Figure 2.** Kaplan-Meier survival curves of 60 HCC patients with different tumor sizes before TACE. Tumor size is related with patient survival. Patients with tumor size >5 cm exhibited significantly poorer survival than did those with tumor size ≤5 cm (log-rank test,  $P < 0.001$ ).

significant difference was shown in Kaplan-Meier survival curves: the patients with sMICA levels >1 ng/mL plus tumor size >5 cm survived significantly shorter than did other patients ( $P < 0.001$ )(Figure 3). Furthermore, The Cox risk model analysis showed that the serum sMICA level was an independent prognostic factor for advanced HCC patients (Table 2).

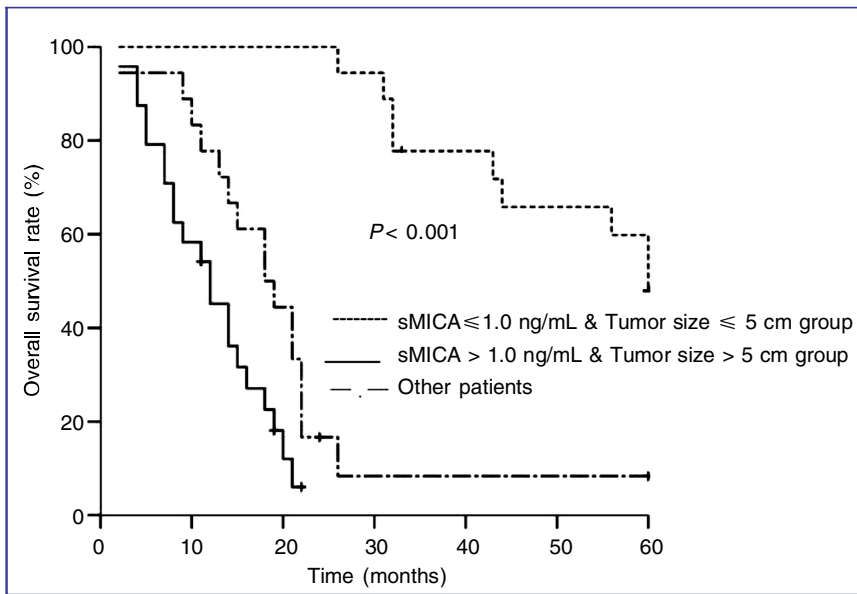
**Correlation of sMICA levels and the proportion of CD56<sup>+</sup>NKG2D<sup>+</sup> peripheral blood lymphocytes**

The levels of CD56<sup>+</sup>NKG2D<sup>+</sup> NK cells ranged from 11.2% to 55.4%. In addition, we analyzed the relationship of changes between sMICA and NKG2D expression on peripheral blood lymphocytes in HCC patients. Pearson

correlation analysis demonstrated that the sMICA level was not significantly correlated with the ratio of total NKG2D<sup>+</sup> cells (coefficient, 0.034;  $P = 0.848$ ) or CD3<sup>+</sup>NKG2D<sup>+</sup> cells (coefficient, -0.097;  $P = 0.585$ ). In contrast, the sMICA level was negatively correlated with the ratio of CD56<sup>+</sup>NKG2D<sup>+</sup> cells (coefficient, -0.421;  $P < 0.001$ )(Figure 4). This result suggests that sMICA may inhibit NK cell function by down-regulating NKG2D expression.

**Discussion**

Growing evidence suggests that MICA plays an

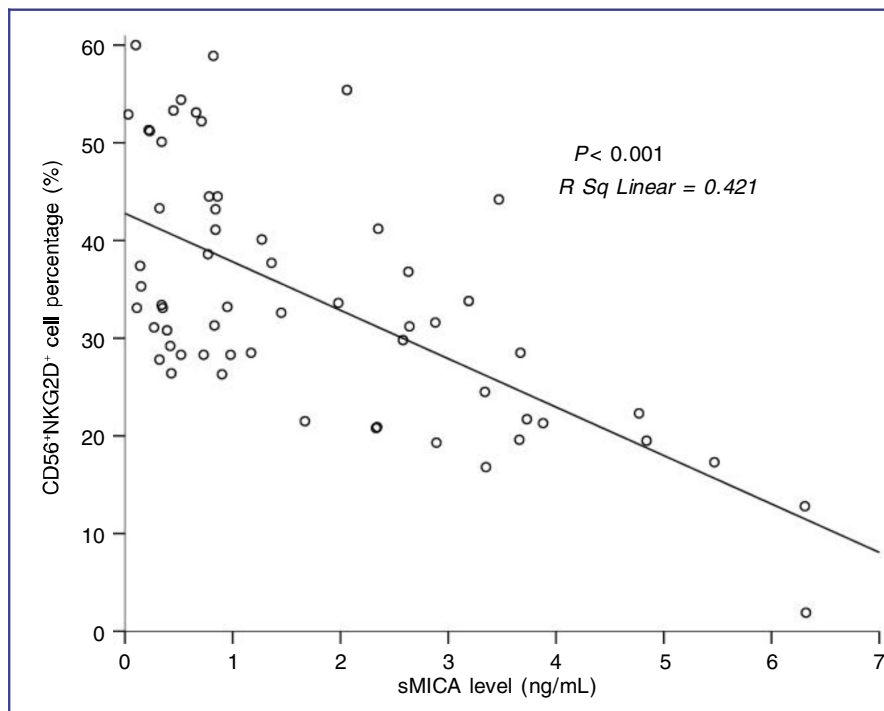


**Figure 3.** Kaplan-Meier survival curves of 60 HCC patients with different serum sMICA levels and tumor sizes before TACE. High sMICA level plus large tumor size is related with short survival time, whereas low sMICA level plus small tumor size is related with long survival time (log-rank test,  $P < 0.001$ ).

**Table 2.** Univariate and multivariate analysis of overall survival in patients with advanced HCC

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Gender	0.886	0.264-2.979	0.845			
Age	1.49	0.633-3.508	0.362			
Serum AFP	1.289	0.836-1.988	0.251			
Serum HBV-DNA	0.744	0.333-1.666	0.473			
Tumor size	3.090	1.116-8.551	0.030	2.942	1.048-8.258	0.040
No. of lesions	2.090	0.916-4.744	0.080			
Cirrhosis	0.844	0.348-2.048	0.708			
Vascular invasion	3.037	0.374-24.312	0.295			
sMICA level	1.534	1.145-2.005	0.004	1.471	1.107-1.954	0.008

HR, hazard ratio; CI, confidence interval.



**Figure 4. Correlation between serum sMICA levels and NKG2D expression on NK cells.** The sMICA level was negatively correlated with NKG2D expression on CD56<sup>+</sup> NK cells in patients with advanced HCC ( $P < 0.001$ ).

important role in tumor immunity. As a glycoprotein, MICA is expressed on the membrane of a variety of cells [6,17]. It is a natural ligand for NKG2D on a variety of immune cells, including a majority of CD56<sup>+</sup> NK cells and some CD8<sup>+</sup> T cells. The binding of MICA to NKG2D strongly activates NK cells and synergistically stimulates T cells [16]. Such stimulation consequently enhances the cytotoxicity of NK cells and CD8<sup>+</sup> T cells and leads to the release of multiple cytokines. Unlike classic MHC-I molecules, MICA is rarely expressed by normal cells but is highly expressed in carcinoma cells, such as HCC [19], prostate cancer [20], glioma [21], and others. Armeanu *et al.* [22] detected significantly high MICA levels in liver tumor tissues but failed to detect MICA expression in normal liver tissues. In addition to the membrane-bound type, MICA can also be shed from the carcinoma cell surface and enter the blood stream to form the soluble type [10].

In line with previous studies, our results demonstrated that sMICA was present in the serum of HCC patients. We found that sMICA level was significantly related with tumor size, indicating that sMICA is closely related to HCC progression. Similar results have also been observed in cervical, breast, and prostate cancers [23–26]. Consistent with our results, studies from Kohga's team suggested that serum sMICA may be tightly related with the condition of HCC patients. Serum sMICA level increased when the condition of the patient deteriorated, whereas sMICA level decreased when the condition of the patient improved with TACE treatment [27].

The mechanism underlying the relationship of serum sMICA levels with carcinoma progression may be related to molecular changes that occur in that process. More specifically, as the degree of tumor malignancy increases, the membrane-bound MICA may be easily shed from the carcinoma cell surface by matrix metalloproteinases such as a disintegrin and metalloproteinase 10 (ADAM10). Then, the soluble type of MICA could enter the blood stream and subsequently damage the anti-cancer function of the MICA-NKG2D pathway [9,23].

In our study, we followed 60 patients with HCC for more than 5 years. The Kaplan-Meier survival curves suggested that the serum sMICA level was significantly related with prognosis: patients with high sMICA levels had a poor prognosis. Cox regression analysis suggested that sMICA may be an independent prognostic factor. Studies on ovarian cancer by Li *et al.* [11], oral squamous cell carcinoma by Tamaki *et al.* [12], and multiple myeloma by Jinushi *et al.* [13] also demonstrated similar results. Therefore, serum sMICA can be used as a valuable prognostic factor for a variety of tumors, including HCC.

To further investigate the function of sMICA in tumor immunity, we analyzed the correlation between the serum sMICA level and the ratio of NKG2D<sup>+</sup> NK cells in the peripheral blood lymphocytes of HCC patients. We found that the serum sMICA level in HCC patients was negatively correlated with the ratio of CD56<sup>+</sup>NKG2D<sup>+</sup> NK cells in the blood. However, serum sMICA level was not

correlated with the ratio of other lymphocytes, such as CD3<sup>+</sup>NKG2D<sup>+</sup> cells. These results suggest that serum sMICA affects the expression of NKG2D in NK cells but not in T lymphocytes of HCC patients. Therefore, sMICA could induce carcinoma cells to escape immune surveillance by damaging NK cell function<sup>[9,10]</sup>.

Despite providing these findings, our study was limited by several factors. (1) There were only 60 patients with unresectable HCC, which seemed insufficient to identify a serum prognostic marker. (2) sMICA levels were not assessed after treatment. These results could provide important information on the influence of treatment on changes in sMICA levels. (3) sMICA levels were not compared with other common serum prognostic markers such as AFP, though such a test may reduce the credibility of sMICA as an independent prognostic factor.

In conclusion, levels of serum sMICA can be used

as an independent prognostic factor for advanced HCC. A high sMICA level reduces NK cell function by decreasing the expression of activating receptor NKG2D in NK cells, which subsequently damages the immune function of HCC patients and eventually causes tumor immune escape. Therefore, it may be necessary to apply immunotherapy for advanced HCC patients, especially for those with high level of sMICA.

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