Prognostic significance of plasma chemerin levels in patients with gastric cancer

Jian Zhang, Hui-Cheng Jin, A-Kao Zhu, Rong-Chao Ying*, Wei Wei, Fang-Jie Zhang

Department of Gastroenterological Surgery, The Hangzhou First People's Hospital, Nanjing Medical University Affiliated Hangzhou Hospital, 261 Huansha Road, Hangzhou 310006, China

ARTICLE INFO

ABSTRACT

Chemerin is a novel adipokine, which is linked to adipogenesis and chemotaxis of the innate immune system. This study aimed to evaluate the relationship between preoperative plasma chemerin level and prognosis of gastric cancers. One hundred ninety-six patients and 196 age- and gender-matched healthy individuals were recruited. Fasting venous blood samples were collected 2 days prior to surgery for the gastric cancer patients and at the physical examination day for the healthy volunteers. Recorded clinico-pathological information included invasion depth, lymph node metastasis, distant metastasis, peritoneal dissemination, tumor size and tumor-node metastasis stage. Plasma chemerin levels were determined using enzyme-linked immunosorbent assay. Plasma chemerin levels were statistically significantly in all patients than in healthy controls (53.1 ± 19.0 ng/mL vs. 31.3 ± 11.3 ng/mL; $P < 0.001$). And it was identified as an independent predictor for 5-year mortality [odds ratio (OR), 2.718; 95% confidence interval (CI), 1.201–4.229; $P = 0.005$] and adverse event (OR, 2.982; 95% CI, 1.223–4.879; $P = 0.003$) of gastric cancer, and had high area under receiver operating characteristic curve (AUC) for prediction of 5-year mortality (AUC, 0.808; 95% CI, 0.745–0.860) and adverse event (AUC, 0.787; 95% CI, 0.723–0.842). It also emerged as an independent predictor for overall survival (Hazard ratios, 1.788; 95% CI, 1.200–2.663; $P = 0.002$) and disease-free survival (Hazard ratios, 2.016; 95% CI, 1.312–3.125; $P = 0.004$). Thus, our results suggest that high plasma chemerin levels are associated with long-term poor prognosis and survival of gastric cancer as well as may play a role as prognostic biomarker in gastric cancer survival.

© 2014 Elsevier Inc. All rights reserved.

1. Introduction

Gastric cancer is one of the most common cancers worldwide and has the second leading cancer-related mortality rate with much poorer survival [7,8]. At present, the only prognostic system routinely employed for the management of gastric cancer is based on the international Union Against Cancer tumor-node metastasis (TNM) staging system [6]. Currently, using clinical parameters alone, we cannot accurately predict the clinical outcome of patients after surgery [29]. The discovery of molecular biological prognostic factors may aid in a more accurate prediction of clinical outcome of patients with gastric cancer [16].

Chemerin, named also as tazarotene-induced gene protein 2 or retinoic acid receptor responder protein 2, is a novel adipokine, which is linked to adipogenesis and chemotaxis of the innate

immune system [2,21]. Interestingly, a few studies have showed that the expression of chemerin is dysregulated in several types of tumors. Chemerin expressions are downregulated in melanoma [18], skin squamous cell carcinoma [32], lung carcinoma [31], and hepatocellular carcinoma [12] compared with matched nontumor tissues and are associated with poor differentiation. However, other studies demonstrate that the expressions of chemerin are upregulated in grade III/IV glioma tissues compared with grade II ones or brain samples from patients with epilepsy [28] and overexpression of chemerin in squamous cell carcinoma of the oral tongue is correlated with tumor angiogenesis and poor clinical outcomes of patients [27]. Recent research has shown chemerin can increase invasiveness of gastric cancer cells and the elevation of serum chemerin level is associated with advanced clinical stages and nonintestinal type of gastric cancer [26]. Thus, circulating chemerin level may be a promising prognostic tool in gastric cancer. The aim of this study was to evaluate prognostic significance of the plasma chemerin level in gastric cancer.

---

* Corresponding author. Tel.: +86 0571 56006911.
E-mail address: dlxedsgd@163.com (R.-C. Ying).

2. Materials and methods

2.1. Study population

This study evaluated 196 patients with pathologically proven gastric cancer receiving treatment at Department Of General Surgery, the Hangzhou First People's Hospital, Hangzhou, China between February 2007 and December 2008. None of these patients had previous malignant diagnoses, concurrent malignancies, or chemotherapy prior to surgery. In addition, 196 age- and gender-matched healthy individuals were recruited as controls. The study protocol was approved by the Medical Ethics and Human Clinical Trial Committee of the Hangzhou First People's Hospital. Written informed consent was obtained from the study subjects or their relatives.

2.2. Assessment

Recorded information included age, gender, invasion depth, lymph node metastasis, distant metastasis, peritoneal dissemination, tumor size and TNM stage. After surgery, patients were followed up every 3 months for 3 years and thereafter every 6 months for 2 years. Adverse event was defined as first local recurrence, distant metastasis, second primary cancer of another organ, or death from any cause during follow-up. Disease-free survival (DFS) was defined as the time between surgery and the date of adverse event. Overall survival (OS) was defined from surgery to death for any cause.

2.3. Immunoassay methods

Venous blood samples were collected 2 days prior to surgery for the gastric cancer patients and at the physical examination day for the healthy volunteers, and then were centrifuged at $1500 \times g$ for 20 min. Plasma samples were stored at -70°C until the day of the analysis. Plasma chemerin levels were measured in duplicate using a commercial enzyme immunoassay kit (Millipore, USA) according to manufacturer's instructions. The person carrying out the assays was completely blinded to the clinical information.

2.4. Statistical analysis

All statistical analyses were performed with SPSS 19.0 (SPSS Inc., Chicago, IL, USA) and MedCalc 9.6.4.0. (MedCalc Software, Mariakerke, Belgium). All quantitative or categorical variables were expressed as the mean ± standard deviation or the number (percentage) respectively, unless otherwise stated. Chi-square tests and t tests were performed for intergroup comparisons as appropriate. A binary logistic-regression model was configured to analyze associations of chemerin to death and adverse event with odds ratio (OR) and 95% confidence interval (CI). A receiver operating characteristic (ROC) curves analysis was used to evaluate the predictive values of chemerin levels for death and adverse event with calculated area under curve (AUC). OS and DFS were estimated using the Kaplan–Meier method and the intergroup differences in survival time were tested using the log-rank test. Multivariate Cox's proportional hazard analysis was carried out to identify independent prognostic factors for OS and DFS with hazard ratios (HR) and 95% CI. All significant parameters in the univariate analysis were entered into a multivariate model. Statistical significance was defined as P values less than 0.05.

Table 1
The tumor clinicopathological parameters of gastric cancer patients.

Characteristics	Number of patients	%
Age		
≥60 y	87	44.4
<60 y	109	55.6
Gender		
Male	112	57.1
Female	84	42.9
Pathological diagnosis		
Adenocarcinoma	160	81.6
Signet-ring cell carcinoma	17	8.7
Others	19	9.7
Tumor size		
<5 cm	132	67.3
≥5 cm	64	32.7
Invasion depth		
T1	21	10.7
T2	41	20.9
T3	52	26.5
T4	82	41.9
Lymph node metastasis		
N0	46	23.5
N1	24	12.2
N2	52	26.5
N3a	44	22.5
N3b	30	15.3
Distant metastasis		
M0	133	67.9
M1	63	32.1
Peritoneal dissemination		
Positive	38	19.4
Negative	158	80.6
Tumor node metastasis stage		
I	50	25.5
II	46	23.5
III	57	29.1
IV	43	21.9
Plasma chemerin level		
High chemerin level	84	42.9
Low chemerin level	112	57.1

3. Results

3.1. Study population characteristics

This study included 196 patients with gastric cancer and 196 age- and gender-matched healthy controls. In addition, there was not statistically significant difference in body mass index between patients and healthy controls (23.0 ± 3.1 kg/m^2 vs. 23.4 ± 3.5 kg/m^2; $P = 0.215$). Table 1 showed the tumor clinicopathological parameters of patients with gastric cancer. Plasma chemerin levels were statistically significantly in all patients than in healthy controls (53.1 ± 19.0 ng/mL vs. 31.3 ± 11.3 ng/mL; $P < 0.001$) and this difference was major. In addition, plasma chemerin levels were bifurcated at mean value. High or low chemerin level indicated more or less than mean value. Thus, 84 patients had high chemerin level and 3 healthy controls had high chemerin level. This intergroup difference was statistically significant using Chi-square test ($P < 0.001$).

3.2. Mortality prediction

136 patients died within 5 years after surgery. Table 2 showed that 5-year mortality was associated with some risk factors including tumor size, invasion depth, lymph node metastasis, distance metastasis, peritoneal dissemination, TNM stage and plasma chemerin level. A multivariate analyses selected plasma chemerin level (OR, 2.718; 95% CI, 1.201–4.229; $P = 0.005$), tumor size (OR, 3.410; 95% CI, 1.901–6.584; $P = 0.003$), peritoneal dissemination