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Elevated plasma visfatin levels correlate with poor prognosis of gastric cancer patients

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ABSTRACT

Visfatin is a proinflammmatory cytokine with accumulating evidence for its rise in circulation of cancer patients. This study aimed to evaluate the relationship between preoperative plasma visfatin level and prognosis of gastric cancers. Preoperative plasma visfatin levels of 262 patients with gastric cancers and plasma visfatin levels of 262 healthy individuals were determined using enzyme-linked immunosorbent assay. Preoperative plasma visfatin level was substantially higher in patients than in healthy subjects. Plasma visfatin levels were associated with invasion depth, lymph node metastasis, distant metastasis, peritoneal dissemination, tumor size and tumor node metastasis stage. Multivariate analysis revealed that high plasma visfatin level was an independent factor for death. Receiver operating characteristic curve analysis showed that plasma visfatin level predicted death with high area under curve. Multivariate Cox regression analysis identified plasma visfatin level as an independent predictor of overall survival. Thus, our results suggest that high preoperative plasma visfatin level is associated with prognostic factors for gastric cancer as well as may play a role as prognostic biomarker in gastric cancer survival.

Introduction

Gastric cancer is the fourth most prevalent malignant cancer worldwide and is the second most frequent cause of cancer death [13]. Prognosis of gastric cancer is associated with many parameters including invasion depth, lymph node metastasis, distant metastasis, peritoneal dissemination, tumor size and tumor node metastasis stage [10,14,28]. Visfatin is an adipokine identified in 2004 and thus named for the suggestion that it would be predominantly produced and secreted in visceral fat [8]. Visfatin is highly preserved across animal evolution. It has a molecular weight of 52 kDa and its gene encodes 491 aminoacids [23]. It is identical to pre-B cell colony-enhancing factor, described in 1994 as a cytokine produced by lymphocytes, acting on lymphocyte maturation and inflammatory regulation [16,21]. Visfatin was also soon recognized as the formerly described nicotinamide phosphoribosyltransferase, the limiting enzyme in nicotinamide adenine dinucleotide biosynthesis [11]. It plays an important role in the inflammation, in a variety of metabolic and stress responses as well as in the cellular energy metabolism [5,12,18,30]. Visfatin has been recently found to be over-expressed and important in the carcinogenesis in several types of cancers [3,15,24,26]. Visfatin is also over-expressed in established gastric cancer cells and human gastric cancer tissues [2]. Moreover, high plasma visfatin level is reported to gradually increase with stage progression of gastric cancer [19]. Thus, plasma visfatin level may be a promising prognostic tool in gastric cancer. The aim of this study was to identify circulating visfatin level in patients with gastric cancer, and evaluate the relation of the visfatin expression and clinicopathological features and their prognostic significance.

Materials and methods

Study population

This study evaluated 262 patients with pathologically proven gastric cancer receiving treatment at Department of Oncological Surgery, Yinzhou People's Hospital, Ningbo, China between February 2006 and May 2008. This study had excluded the patients who had previous malignant diagnoses, concurrent malignancies, or secondary tumors as well as who had missing of follow-up, unavailable blood sample and incomplete clinical information. This

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study also included 262 age- and gender-matched healthy controls. The study protocol was approved by the Chinese Ethics Committee of Human Resources at the Yinzhou People's Hospital. Written informed consent was obtained from the study subjects.

Assessment

This study collected information on demographic factors and clinical information on the patients with respect to invasion depth, lymph node metastasis, distant metastasis, peritoneal dissemination, tumor size and tumor node metastasis stage. All patients received radical gastrectomy, palliative gastrectomy or exploratory laparotomy. Adjuvant treatment with chemotherapy was based on international guidelines.

After surgery, patients were followed up every 3 months for 3 years and thereafter every 6 months for 2 years. Overall survival was defined as the interval between the dates of surgery and either the time of the last follow-up or death due to gastric cancer. Censoring occurred for patients still alive or deceased as a result of other reasons at the last follow-up.

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. Venous blood samples were placed on ice. After centrifugation ($1500 \times g$ for 20 min), plasma samples were stored at $-70\,^{\circ}C$ until assayed. Plasma visfatin levels were measured using a commercial enzyme immunoassay kit (Phoenix Pharmaceuticals, Belmont, CA) according to manufacturer's instructions. All samples were assayed in duplicate. The person carrying out the assays was completely blinded to the clinical information.

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 variables were expressed as the mean ± standard deviation, unless otherwise stated. Categorical variables were expressed as the number (percentage). Chi-square tests and *t* tests were performed for intergroup comparisons. To analyze association of visfatin to death, multivariate analysis was performed in a binary logistic-regression model with calculated odds ratio (OR) and 95% confidence interval (CI). The predictive performance of visfatin levels for death was evaluated using a receiver operating characteristic (ROC) curves analysis with calculated area under curve (AUC). The sensitivities and specificities were calculated using a cut-off value that was selected from the ROC curve. Overall survival was 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 compare and identify independent prognostic factors for overall survival and to calculate hazard ratios (HR) and 95% CI. All significant parameters in the univariate analysis were entered into a multivariate model. All *P* values less than 0.05 were considered as statistically significant with a 2-tailed test.

Results

Change of plasma visfatin levels in gastric cancer patients

This study included 262 gastric cancer patients and 262 sex- and age-matched healthy individuals. Table 1 shows clinical information on the patients with gastric cancers. Fig. 1 found that plasma visfatin levels were markedly higher in all patients than in healthy controls.

Table 1
The tumor clinicopathological variables of gastric cancer patients.

Characteristics	Number of patients	%
Age		
≥60 years	121	46.2
<60 years	141	53.8
Gender		
Male	156	59.5
Female	106	40.5
Pathological diagnosis		
Adenocarcinoma	214	81.7
Signet-ring cell carcinoma	22	8.4
Others	26	9.9
Tumor size		
<5 cm	182	69.5
≥5 cm	80	30.5
Invasion depth		
T1	25	9.5
T2	42	16.0
T3	67	25.6
T4	128	48.9
Lymph node metastasis		
N0	82	31.3
N1	38	14.5
N2	47	17.9
N3a	60	22.9
N3b	35	13.4
Distant metastasis		
M0	186	71.0
M1	76	29.0
Peritoneal dissemination		
Positive	50	19.1
Negative	212	80.9
Tumor node metastasis stage		
I	47	17.9
II	60	22.9
III	78	29.8
IV	77	29.4

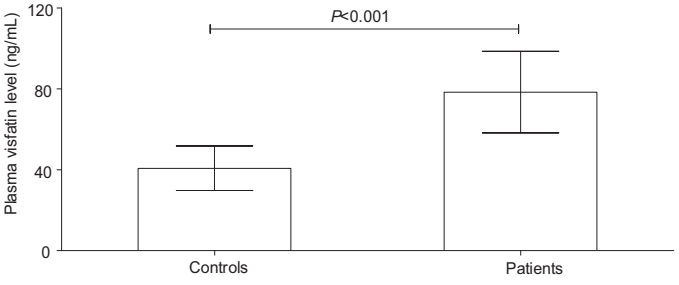

Fig. 1. The change of plasma visfatin levels in gastric cancer patients compared with healthy controls. Intergroup difference was analyzed using *t* test.

Relationship between plasma visfatin levels and clinicopathological characteristics

In this study, plasma visfatin levels were bifurcated at mean value (78.4 ng/mL). Values of >78.4 ng/mL indicated high levels of plasma visfatin, and values of <78.4 ng/mL indicated low levels of plasma visfatin. In Table 2, it was found that high plasma visfatin levels were significantly correlated with invasion depth, lymph node metastasis, distant metastasis, peritoneal dissemination, tumor size and tumor node metastasis stage.

Death prediction in gastric cancer patients

Table 3 shows the some risk factors were correlated with 5-year mortality of patients with gastric cancer during follow-up.