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Original article

The preoperative plasma fibrinogen level is an independent prognostic factor for overall survival of breast cancer patients who underwent surgical treatment

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ABSTRACT

Background: Previous studies have suggested that plasma fibrinogen contributes to tumor cell proliferation, progression and metastasis. The current study was performed to evaluate the prognostic relevance of preoperative plasma fibrinogen in breast cancer patients.
Method: Data of 2073 consecutive breast cancer patients, who underwent surgery between January 2002 and December 2008 at the Sun Yat-sen University Cancer Center, were retrospectively evaluated. Plasma fibrinogen levels were routinely measured before surgeries. Participants were grouped by the cutoff value estimated by the receiver operating characteristic (ROC) curve analysis. Overall survival (OS) was assessed using Kaplan–Meier analysis, and multivariate Cox proportional hazards regression model was performed to evaluate the independent prognostic value of plasma fibrinogen level.
Results: The optimal cutoff value of preoperative plasma fibrinogen was determined to be 2.83 g/L. The Kaplan–Meier analysis showed that patients with high fibrinogen levels had shorter OS than patients with low fibrinogen levels ($p < 0.001$). Multivariate analysis suggested preoperative plasma fibrinogen as an independent prognostic factor for OS in breast cancer patients (HR = 1.475, 95% confidence interval (CI): 1.177–1.848, $p = 0.001$). Subgroup analyses revealed that plasma fibrinogen level was an unfavorable prognostic parameter in stage II–III, Luminal subtypes and triple-negative breast cancer patients.
Conclusion: Elevated preoperative plasma fibrinogen was independently associated with poor prognosis in breast cancer patients and may serve as a valuable parameter for risk assessment in breast cancer patients.

Introduction

Breast cancer is by far the most common cancer and the main cause of cancer death in women worldwide. According to the National Cancer Institute, there were more than 230,000 cases of female breast cancer in 2014, and more than 40,000 women have died of breast cancer [1]. The prognosis of breast cancer patients is influenced by numerous factors, such as TNM staging, intrinsic subtypes, age, and gender [2,3]. Recurrence and metastasis remain a great challenge for cure despite the excellent outcomes of early-stage breast cancer after standard treatments [4].

Recently, much attention has been given to the association between hypercoagulation and the progression of malignancies. Increasing data indicated that the members of the coagulation cascade are activated during cancer progression, and associated with tumor stage, response to chemotherapy and prognosis [5]. Fibrinogen is one of the important indicators of coagulation. It is a 340-kDa glycoprotein mainly synthesized by hepatocytes and converted to insoluble fibrin by activated thrombin [6,7].

Fibrinogen is involved in a number of biological processes that are regulated by different cytokines, such as vascular endothelial growth factor (VEGF), interleukin-1 (IL-1) beta, and fibroblast

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growth factor (FGF) −2 [8–10]. Previous research has demonstrated that an increased level of plasma fibrinogen is frequently observed in cancer patients and that fibrinogen plays a vital role in tumorigenesis and progression, including stroma formation, angiogenesis, and hematogenous metastasis [11,12]. Elevated level of preoperative plasma fibrinogen has been associated with poor prognosis in patients with malignancies, such as lung cancer [13,14], colorectal cancer [15,16], pancreatic cancer [17], prostate cancer [18] and renal cell carcinoma [19].

However, few studies have evaluated the significance of preoperative plasma fibrinogen level in breast cancer patients as a predictor of survival after surgical treatment. The aim of this retrospective clinical study was to investigate the association between the plasma fibrinogen level and the prognosis of breast cancer patients.

Materials and methods

Study population

Patients with histologically diagnosed of breast cancer between January 2002 and December 2008 in the Sun Yat-sen University Cancer Center (SYSUCC) were retrospectively reviewed. Other inclusion criteria were as follows: (1) received surgical treatment and (2) female patients. Exclusion criteria were as follows: (1) received neoadjuvant chemotherapy before surgery; (2) received surgical treatment before admission; (3) with previous or coexisting cancers other than breast cancer; (4) confirmed metastasis; (5) concomitant conditions influencing plasma fibrinogen level, such as liver disease, blood coagulation disorders and daily antiplatelet or anticoagulant treatment before surgery; (6) not enough data can be extracted. All patients were followed up to December 31, 2014 or until death from any cause.

Clinical data collection

Baseline characteristics including age, menstrual status, pathological diagnosis, histologic grade, axillary lymph node status, hormone receptor and human epidermal growth factor receptor-2 (HER-2) status, surgery type, family history, date of last follow-up or death and preoperative plasma fibrinogen level were collected. Fibrinogen levels were measured as part of the routine clinical evaluation prior to surgery by the Clauss method using Dade Thrombin Reagent™ and a Sysmex CA-7000 automated coagulometer (Sysmex, Kobe, Japan). Plasma fibrinogen levels between 1.80 and 4.00 g/L were considered to be normal. The clinical stages of the disease were determined by TNM staging system according to the AJCC, and the cancer subtypes were classified as follows: Luminal A subtype (estrogen receptor positive (ER+) and progesterone receptor positive (PR+), HER-2−), luminal B subtype (ER+ and/or PR+, HER-2+), HER-2 overexpressing subtype (ER−, PR−, HER-2+) and triple-negative subtype (ER−, PR−, HER-2−). The follow-up of patients was performed through outpatient medical records, telephone or letters by the “Department of Follow-up & Medical Record Management”.

Statistical analyses

Preoperative plasma fibrinogen values were expressed using mean and standard deviations (SD), and categorical data were described using numbers and percentages. Kolmogorov–Smirnov test was performed to test the normal distribution of the data. The correlation between patients' characteristics and preoperative plasma fibrinogen was evaluated by unpaired *t*-test or one-way analysis of variance (ANOVA), and differences between categories were examined using the Chi-squared test. The endpoint assessed was overall survival (OS), calculated from the time of pathological diagnosis to date of death from any cause or the last follow-up. SPSS 19.0 (SPSS Inc., Chicago, IL, USA) was used to perform all statistical analyses in the present study. The clinical significance and the cutoff value for the continuously coded variable preoperative plasma fibrinogen level were determined by the ROC curve analysis, and patients were categorized into two groups according to the cutoff value to assess the risk of death. Kaplan–Meier method was carried out for survival analyses and the differences between the groups were assessed by log-rank test. Factors examined in the univariate analysis were age (≤35 vs. >35 years), menstrual status, tumor type, histologic grade, tumor size, lymph node status, hormone receptor status, HER-2 status, surgical method, family history and plasma fibrinogen level. Univariate and multivariate analyses (Cox proportional hazards model) were performed to identify the independent variables associated with OS. Hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) estimated from the Cox analysis were regarded as relative risks, and a two-tailed p value < 0.05 was considered significant.

Results

Patient characteristics

A total of 2073 consecutive patients with histopathologically diagnosed breast cancer in SYSUCC were enrolled after eligibility review. The selection process is shown in Fig. 1. The median follow-up time was 75 months (range 3–143 months), and death occurred in 329 (15.9%) of the 2073 breast cancer patients. The median age of the enrolled patients was 49.0 years (range: 22–96 years), and 189 (9.1%) patients were aged below 35 years. Patient characteristics and correlations between preoperative plasma fibrinogen level and clinicopathological parameters are shown in Table 1. The mean level of preoperative plasma fibrinogen level was 2.88 ± 0.68 g/L, and it was associated with age and menstrual status (both $p < 0.001$, Table 1). Middle-aged and elderly (>35 years old) and postmenopausal patients had higher preoperative plasma fibrinogen level. No correlation was observed between fibrinogen level and histologic grades, tumor size, lymph node status, hormone receptor status, HER-2 status and family history (all $p > 0.05$). Moreover, patients who experienced poor outcome had significantly increased preoperative fibrinogen level compared to patients with better prognosis ($p < 0.001$).

Cutoff value of preoperative plasma fibrinogen

ROC curve analysis was performed to determine the optimal cutoff value of preoperative plasma fibrinogen level. The area under

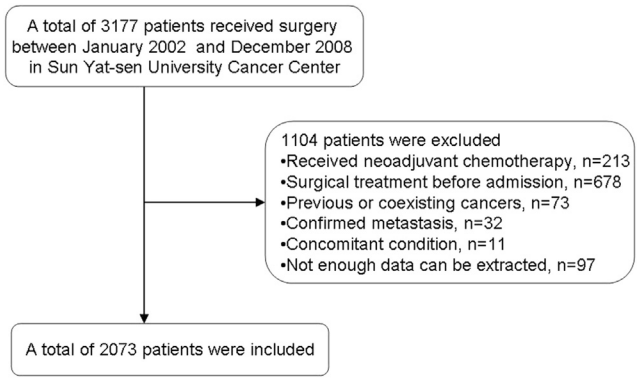

Fig. 1. Flow chart of the patient selection.