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Serum transthyretin level is associated with prognosis of patients with gastric cancer

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ARTICLE INFO

Article history:
Received 14 December 2017
Received in revised form
18 January 2018
Accepted 15 February 2018
Available online xxx

Keywords:
Gastric cancer
Prognosis
Transthyretin
Prealbumin
Malnutrition
Overall survival

ABSTRACT

Background: The goal of the present study was to determine whether serum transthyretin level can be used as a novel prognostic biomarker for patients with gastric cancer.
Patients and methods: Serum levels of transthyretin were examined before treatment in 42 patients with gastric cancer, 30 of whom underwent curative operation and had their prognostic factors analyzed.
Results: In an analysis using a receiver operating characteristic curve, transthyretin was evaluated as a useful biomarker to predict the overall survival of the patients ($P = 0.033$), and a level of 22.8 mg/dL was determined as the cut off value. The transthyretin levels exhibited statistically significant correlations with total protein ($r = 0.598$, $P < 0.001$), albumin ($r = 0.626$, $P < 0.001$), and retinol binding protein ($r = 0.753$, $P < 0.001$). On the other hand, the transthyretin levels showed statistically significant inverse correlations with tumor size ($r = -0.753$, $P < 0.001$) and the numbers of involved lymph nodes ($r = -0.453$, $P = 0.012$). The patients with serum transthyretin levels of <22.8 mg/dL showed poorer prognosis than those with levels of ≥22.8 mg/dL ($P = 0.033$); therefore, serum transthyretin level was an independent prognostic factor for the gastric cancer patients (hazard ratio: 0.420, 95% confidence interval: 0.180–0.985, $P = 0.042$).
Conclusions: Anthropometric measurement of serum transthyretin can be useful for predicting the prognosis of patients with gastric cancer.

Introduction

Although gastric cancer is the world's fourth most common cancer, its age-standardized incidence and mortality rates have been decreasing in both men and women in Japan,[1,2] where many treatment modalities have been developed to improve the prognosis of patients. However, gastric cancer remains the third leading cause of cancer death in Japan.[2,3]

In search of a prognostic factor independent of tumor staging, there has been accumulating evidence that inflammation- or nutritional factor–based prognostic scores, such as the Glasgow Prognostic score based on C-reactive protein (CRP) and albumin, are useful in predicting patient prognosis.[4]

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0022-4804/$ – see front matter
https://doi.org/10.1016/j.jss.2018.02.035

We previously reported the significance of increased levels of vascular endothelial growth factor, which affects nutritional and immunological status. On the other hand, transthyretin (TTR), also known as prealbumin, has a relatively short half-life (approximately 2 d) and is the earliest laboratory indicator of malnutrition status, as it contains a high percentage of essential amino acids.[5] TTR correlates with patient outcome in various diseases.[6-8] TTR has been reported to be a useful diagnostic marker for gastric cancer,[9] a predictive marker for postoperative complications in gastric cancer surgery,[10] and a predictive marker for metastasis in patients with inoperative gastric cancer.[11] As for preoperative marker-predicting prognosis, Han *et al.*[12] reported on the usefulness of serum TTR level in patients with adenocarcinoma of esophagogastric junction. However, the prognostic value of serum TTR has not yet been determined. Thus, in the present study, we aimed to determine whether serum TTR level can be used as a novel prognostic biomarker for patients with gastric cancer.

Materials and methods

Patients

Forty-two gastric cancer patients were enrolled between February 20, 2011 and August 20, 2013. Among these, 30 patients underwent curative-intent surgery, whereas the remaining 12 patients were excluded due to metastatic disease. After surgery, the final stage of the patients was determined pathologically according to the TNM classification system of malignant tumors published by the International Union Against Cancer, eighth edition.[13] Of the gastric cancer patients, 13 were diagnosed as having stage I, four patients as having stage IIA, one patient as having stage IIB, 11 patients as having stage III, and one patient as having stage IV. Since no patient with stage IV disease showed positive peritoneal cytology, neoadjuvant chemotherapy was performed. The study protocol was approved by the ethics committee of Fukushima Medical University, and written informed consent was obtained from all enrolled patients.

Measurements of TTR and other parameters

Blood samples were collected before the initiation of treatment. Patient nutritional status was determined by measuring the serum concentrations of total protein (TP), albumin, retinol-binding protein (RBP), and TTR, transferrin, as well as a loss of body weight of over 3 kg within 3 mo, and body mass index. These parameters were measured at the Central Clinical Laboratory of Fukushima Medical University Hospital. As for the inflammatory parameters, CRP, white blood cell count, neutrophil and lymphocyte counts, as well as neutrophil-to-lymphocyte ratio, were used.

Statistical analysis

Data are presented as frequencies or percentages for categorical variables and mean ± standard error of the mean for continuous variables, unless otherwise indicated. For categorical clinical variables, differences between the groups were evaluated by Fisher's exact test. The differences in mean values between the groups were analyzed using the Mann–Whitney *U* test. The receiver operating characteristic (ROC) curve was used to evaluate the usefulness of the examined parameters as a prognostic factor. Associations between the two variables were quantified using Spearman's rank correlation coefficient. The mean observation period was 42.9 months (median: 42.9, range: 1.4–74.7), and the final assessment of disease status was made on July 31, 2017. The overall survival rate was calculated using the Kaplan–Meier method, and differences between the groups were assessed by using the log-rank test. Factors found to be significant in the univariate analysis were subjected to multivariate analysis using a Cox proportional hazard model to identify the independent predictors of prognosis. A two-sided *P* value of <0.05 was considered to indicate a statistically significant difference. All statistical calculations were performed using SPSS, version 24 (IBM Japan, Tokyo, Japan).

Results

Analysis using a ROC curve

In an analysis using a ROC curve (Fig. 1), TTR was evaluated as useful biomarker to predict the overall survival of the patients ($P = 0.033$), and a TTR level of 22.8 mg/dL was determined as the cut off value, at which sensitivity was 1.000, and specificity was 0.654. Table 1 shows the patient characteristics according to the TTR value. The incidence of T3 +T4 was statistically higher in the patients with TTR <22.8 mg/dL than in those with ≥22.8 mg/dL ($P = 0.008$). Although there was no statistically significant difference in the status of lymph node metastasis between the two groups, the incidence of stage

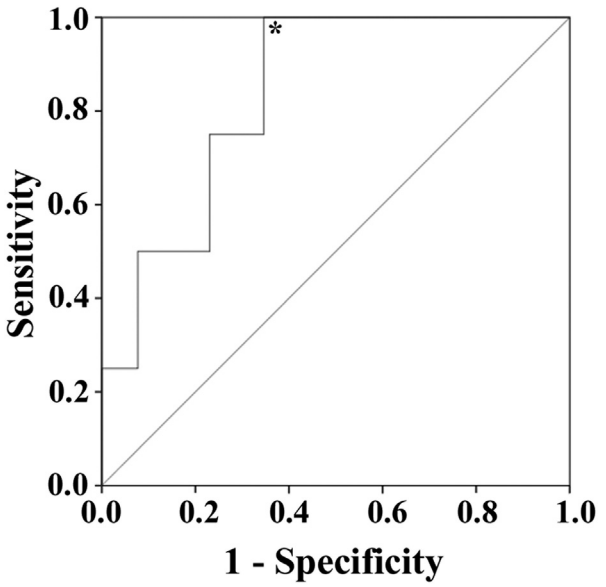

Fig. 1 – Receiver operating characteristic curve for transthyretin. The calculated area under the curve was 0.837. *The coordinate point when the cut off threshold of the transthyretin was set to 22.8 mg/dL.