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A novel scoring system associating with preoperative platelet/lymphocyte and clinicopathologic features to predict lymph node metastasis in early gastric cancer

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ABSTRACT

Background: Precise determination of the lymph node status is critical for determining appropriate treatment for early gastric cancer (EGC). This study attempted to establish a simple, effective risk scoring system to predict lymph node metastasis (LNM) in EGC by investigating the relationship between platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) and EGC LNM.

Materials and methods: We retrospectively reviewed 312 operable patients with EGC. The clinical utility of PLR and NLR was tested by receiver operating characteristic curves. The scoring system was developed using independent risk factors. Finally, 89 EGC patients were collected from prospective database to validate the scoring system's accuracy.

Results: The optimal PLR and NLR cut-off values were 106 and 2.97, respectively. High NLR ($P = 0.009$) and PLR ($P = 0.007$) values were associated with LNM of EGC in univariate analyses, although only high PLR ($P = 0.025$) was an independent risk factor in multivariate analyses, together with age ($P = 0.009$), differentiation ($P = 0.017$), invasive depth ($P < 0.001$), and tumor size ($P = 0.003$). The scoring system's accuracy for retrospective and prospective data was 0.781 (95% confidence interval: 0.721-0.841) and 0.817 (95% confidence interval 0.714-0.920), respectively.

Conclusions: Preoperative PLR and NLR correlate with EGC LNM. Our scoring system is reliable, accurate, and effective in predicting LNM in EGC patients.

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Introduction

Early gastric cancer (EGC) is defined as cancer cells invading the mucosa (T1a) or submucosa (T1b) of the gastric wall, regardless of regional lymph node metastasis (LNM).[1] In the last 50 y, although the incidence of gastric cancer (GC) has been decreasing, the portion of GC diagnosed as clinical early stage has been increasing because of the progress of endoscopic diagnostic technology and other screening programs, especially in Japan and Korea.[2] With improved early diagnosis of GC, the overall survival of EGC has been increasing, but it declines once LNM develops.[3] Currently, compared with traditional invasive treatment ways like laparotomy and laparoscopic resection, minimally invasive approaches to cure EGC, including endoscopic submucosal dissection (ESD) and endoscopic mucosal resection (EMR), have increased in frequency. However, these approaches are contraindicated if LNM is present; hence, gastrectomy with lymphadenectomy is required.[4] In contrast with advanced GC, standard D2 lymphadenectomy is not necessary for EGC without LNM; D1 or D1+ lymphadenectomy could be selected to achieve curative resection.[5] Therefore, to avoid insufficient treatment or overtreatment, it is essential to confirm whether patients with EGC have LNM before choosing the optimal treatment scheme.

To assess for the presence of LNM, some imaging studies, such as axial computed tomography (CT), magnetic resonance imaging, and positron emission tomography–computed tomography (PET-CT), are typically used. However, these tools are still unable to consistently and precisely predict LNM, especially in EGC.[6,7] In addition, some studies reported that several new methods and biomarkers were useful in identifying LNM in GC,[8-10] but considering economic efficiency and feasibility, these techniques are difficult to use widely in the clinic. Therefore, we still lack an effective preoperative biomarker that can be conveniently be put into widespread use for predicting LNM in patients with EGC.

Recently, numerous investigations have demonstrated that the systemic inflammatory response is closely related to tumor progression.[11] Platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR), two novel inflammation-related biomarkers, have been confirmed to be prognostic indicators in epithelial ovarian cancer, esophageal squamous cell cancer, and colorectal neoplasms.[12-14] However, as far as we are aware, no studies have reported the association between PLR, NLR, and LNM in EGC.

Therefore, this study was designed to detect the relationship between PLR and NLR and EGC LNM and to develop a novel, simple, and practical risk scoring system combining inflammation-related variables with other clinicopathologic factors to predict LNM in EGC.

Materials and methods

Patients

We retrospectively collected 649 patients with EGC who underwent curative gastrectomy with standard D1 or D2 lymphadenectomy, confirmed by postoperative pathology, from January 2006 to January 2014 in the First Affiliated Hospital of Wenzhou Medical University, China. The exclusion criteria for this study were (1) fewer than 15 dissected lymph nodes (LNs; the patients were included if the final pathology shown LNM even if lacking enough dissected LNs), (2) hepatocirrhosis or hematological diseases, (3) synchronous and metachronous malignancies, (4) severe infection, and (5) severe connective tissue disease. Most patients (318) were excluded owing to insufficient number of retrieved LNs. In addition, there were three patients with liver cirrhosis, one patient with leucocythemia, four patients with synchronous and metachronous malignancies, 10 patients with severe inflammation (combination of infectious symptoms and white blood cell counts higher than 10×10^9/L), and one patient with systemic lupus erythematosus. Eventually, 312 patients with EGC were included in this study. The clinicopathologic data, including age, sex, tumor location, tumor size, macroscopic types, pathologic type, invasive depth, and postoperative tumor-nodes-metastasis stage, were collected by two reviewers who did not participate in data analysis. Using the same exclusion criteria listed previously, 89 patients with EGC treated between July 2014 and December 2015 were collected as the validation group from our prospective database.

This study was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University. All patients provided written informed consent.

Peripheral blood sample analysis

Patients routinely underwent preoperative hematologic testing. Blood samples were collected in ethylenediaminetetraacetic acid tubes within 7 D before the operation (median time 3.1 D). Routine blood tests were performed by an automated hematology analyzer (XE-2100; Sysmex Co, Kobe, Japan), including measurements of serum albumin, hemoglobin, carcinoembryonic antigen (CEA), and CA19-9 levels, as well as determining white blood cell, neutrophil, lymphocyte, and platelets counts.

Definition and grouping of NLR and PLR

The definition of NLR was the neutrophil count divided by the lymphocyte count, and that of PLR was the platelet count divided by the lymphocyte count. As neither NLR nor PLR have been studied in association with EGC LNM, receiver operating characteristic (ROC) curves were used to determine the most suitable cut-off values in this study.[15] Values with a maximal Youden index were selected. We then divided the patients into two groups according to the cut-off values.

Statistical analysis

All continuous variables are presented as mean ± standard deviation, and the differences between groups were analyzed by *t*-tests. Boxplots were used to present the distribution of NLR and PLR in the lymph node positive group (LNPG) and lymph node negative group (LNNG). The χ^2 test (or Fisher's