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# The value of the combination of hemoglobin, albumin, lymphocyte and platelet in predicting platinum-based chemoradiotherapy response in male patients with esophageal squamous cell carcinoma

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ABSTRACT

*Objective:* The predictive value of HALP in esophageal cancer is currently unclear. We aimed to evaluate the value of HALP in predicting platinum-based definitive chemoradiotherapy response in male patients with esophageal squamous cell carcinoma.

*Methods:* Data from all newly diagnosed patients with esophageal squamous cell carcinoma (ESCC) were collected from January 1, 2010 to December 31, 2014 in Qilu Hospital. The treatment protocol was definitive chemoradiotherapy consisting of docetaxel plus cisplatin or carboplatin. The response assessment of the definitive chemoradiotherapy was based on computed tomography (CT) and barium meal test results.

*Results:* A total of 39 patients were included in the present study. The median value of HALP was 48.34. The chemoradiotherapy response rate of patients in the low HALP value group was 35%, compared with 78.95% of patients in the high HALP group ($P = 0.010$). Additionally, the median progression-free survival in the 2 patient groups was significantly different (10.7 vs. 24.7 m, $P = 0.041$). In the multivariate analysis, patients with HALP higher than 48.34 had longer progression-free survival than patients with HALP of 48.34 or less (HR 2.745; 95% CI, 1.176–6.408; $P = 0.020$). However, there was no significant difference for overall survival between the high HALP group and low HALP group.

*Conclusion:* Our data suggested that pretreatment HALP could predict the platinum-based chemoradiotherapy response of tumors and progression free survival in male patients with ESCC. Therefore, HALP could be used in routine clinical practice to guide the therapeutic strategies for individual treatment in patients with ESCC.

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## 1. Introduction

Esophageal cancer (EC) is the eighth most common malignancy [1]. There were >455,800 new EC cases and 400,200 EC-related deaths worldwide in 2012 alone [2]. Esophageal squamous cell carcinoma (ESCC) is the major histological type of this carcinoma in East Asia and some parts of Europe. The occurrence of EC in China was estimated in 2011 by Zeng H et al., and they reported that ESCC was the most common histological type of EC in China, accounting for 88.84% of patients with EC [3]. Definitive chemoradiotherapy has been considered as the standard treatment for patients with inoperable EC since the results of the RTOG 85-01 trial were released [4]. The RTOG 85-01 trial concluded that chemoradiation treatment with 5-fluorouracil (5-FU) and cisplatin could improve the 5-year survival by 26% compared with radiotherapy alone [5]. A combination of 5-FU with cisplatin and docetaxel with carboplatin are the most commonly used regimens in clinical practice. A study by Honing et al. reported that there was no significant difference in median disease-free survival and overall survival between patients who received 5-FU/cisplatin and paclitaxel/carboplatin. However, the hematological and nonhematological adverse event rates were significantly lower in the paclitaxel/carboplatin group [6]. Another study by Orditura reported that the pathological complete response rate was 30% with a concurrent chemoradiotherapy treatment consisting of weekly paclitaxel and cisplatin with radiotherapy in patients with locally advanced EC [7]. Although improvements have been made in the treatment of EC, the overall survival remains poor because it is usually diagnosed at a late stage. Therefore, it is of vital importance to explore the role of tumor markers in predicting treatment response and survival in EC patients.

Inflammatory responses play an important part in the development of the malignancy [8]. The elevated platelet to lymphocyte ratio (PLR) has been reported to be associated with poor prognosis in gastroesophageal, colorectal, hepatocellular, pancreatic and ovarian cancers [9–10]. Several studies reported that elevated PLR was a biomarker of worse response to platinum-based chemotherapy [11–13]. An association between low hemoglobin concentration and poor tumor control or prognosis was observed in squamous cell carcinoma at several sites

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[14–18]. Albumin level was the main parameter reflecting the nutritional status of the patients. Di Fiore et al. reported that serum albumin of >35 g/L was the only independent factor for predicting response to chemoradiotherapy in patients with EC [19]. According to previous studies, hemoglobin and albumin were positively correlated and PLR was negatively correlated with the prognosis of cancer patients. A retrospective cohort study by Chen et al. reported that HALP was an independent prognostic factor in gastric cancer patients [20]. The HALP value was defined as follows: hemoglobin (g/L) × albumin (g/L) × lymphocyte (/L)/platelet (/L). According to these results, the new parameter HALP seems to be a prognostic marker of platinum-based chemoradiotherapy response and overall survival in theory.

Therefore, the aim of the present study was to examine whether the measurement of pretreatment HALP could function as a parameter to predict platinum-based definitive chemoradiotherapy response and the prognosis in ESCC patients.

## 2. Materials and methods

### 2.1. Patient selection

All newly diagnosed EC patients were retrospectively reviewed from January 1, 2010 to December 31, 2014, in Qilu Hospital, Shandong University, Shandong Province. The inclusion criteria were as follows: (1) sex; male, (2) histology; ESCC, (3) Karnofsky Performance Status (KPS); at least 70, (4) treatment; definitive chemoradiotherapy consisting of docetaxel plus cisplatin or carboplatin, and (5) adequate organ function (including kidneys and liver). Exclusion criteria included previously received chemotherapy, radiotherapy or surgery, distant metastases, and other conditions such as any inflammatory signs or hematological diseases. Informed consents by the patients or the relatives were obtained by telephone. This study conformed to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008) and was approved by the Ethics Committee in Qilu Hospital.

### 2.2. Pretreatment evaluation

Initial evaluation modalities included upper gastrointestinal barium X-ray; endoscopy of the upper gastrointestinal tract and biopsy of the primary tumor; and computed tomography (CT) of the neck, chest, and abdomen. Blood samples were evaluated for complete blood cell count and biochemistry. In addition, an optional $^{18}$F-fluorodeoxyglucose positron emission tomography computed tomography ($^{18}$F-FDG PET/CT) evaluation was conducted. The clinical stage was based on the UICC TNM classification of malignant tumors (2002).

### 2.3. Treatment schedule

Platinum-based chemotherapy was administered concurrently with radiotherapy, starting on day 1. The chemotherapy consisted of intravenous infusion of docetaxel (100–120 mg, day 1) plus intravenous infusion of cisplatin (25 mg/m$^2$/day, day 1–3) or carboplatin (AUC = 5, day 1). Chemotherapy was repeated every 3 weeks. Some patients received another 1 or 2 cycles of chemotherapy after the completion of the radiotherapy. Radiotherapy was delivered using 3-dimensional conformal radiotherapy (3D-CRT). Radiotherapy was administered at 1.8–2.0 Gy per fraction in 28–32 fractions up to total dose of 50.4–64.0 Gy. One fraction was administered daily and 5 fractions were administered from Monday to Friday. Gross tumor volume (GTV) included the primary neoplasm and involved lymph nodes; the clinical target volume (CTV) was defined as having margins from GTV of 3–5 cm proximally and distally, and 0.8 cm circumferentially; the planning target volume (PTV) was the CTV with a 1-cm margin proximally, distally, and circumferentially.

### 2.4. Response and acute toxicity assessment

The response assessment of the definitive chemoradiotherapy was based on CT and barium meal test results when the patients had completed the full-course of radiotherapy and at least 2 cycles of chemotherapy. Definitions of complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) were dependent on the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines [21]. Acute toxicities were assessed according to Common Terminology Criteria for Adverse Events (CTCAE version 4.0) [22]. Follow-up examinations were conducted with CT scanning and barium X-ray every month for the first 6 months, every 3 months for the next 6 months, and every 6 months thereafter.

### 2.5. Statistical analysis

The differences between rates in high and low HALP group were tested by Fisher's exact test. Progression-free survival was defined as the time from the start of the definitive chemoradiotherapy to the date of disease progression, the day of death, or the last day of follow-up. Overall survival was defined as the time from the first day of the definitive chemoradiotherapy to the day of death or the last date of follow-up. The survival curves were constructed with the Kaplan-Meier method and analyzed by log-rank test. Results were considered significant if $P < 0.05$ was obtained. The SPSS software package (version 17.0; SPSS Inc., Chicago, IL, USA) was used for the statistical analysis.

## 3. Results

### 3.1. Patient characteristics

A total of 39 patients were included in the analysis from January 1, 2010 to December 31, 2014. The last follow-up was performed on August 6, 2016, and the median follow-up time was 27.2 months. The patient characteristics are listed in Table 1. The median age was 60 years (range: 45–71 years). The median length of the tumors was

**Table 1**
Clinical and patient characteristics ($n = 39$).

| Characteristic N of patients (%) | | N of patients | | |
|---|---|---|---|---|
| | | HALP[a] ≤ 48.34 ($n = 20$) | HALP[a] > 48.34 ($n = 19$) | *P* value |
| Age, years | | | | 0.751 |
| ≥60 | 21(53.85%) | 10 | 11 | |
| <60 | 18(46.15%) | 10 | 8 | |
| KPS | | | | 0.695 |
| ≥80 | 31(79.49%) | 15 | 16 | |
| 70 | 8(20.51%) | 5 | 3 | ` |
| Location | | | | 1.000 |
| Cervical and upper thoracic | 14(35.90%) | 7 | 7 | |
| Middle and lower thoracic | 25(64.10%) | 13 | 12 | |
| Length | | | | 0.111 |
| ≥6 cm | 22(56.41%) | 14 | 8 | |
| <6 cm | 17(43.59%) | 6 | 11 | |
| Stage | | | | 1.000 |
| II and III | 22(56.41%) | 11 | 11 | |
| $IV_A$ | 17(43.59%) | 9 | 8 | |
| Chemotherapy cycle | | | | 0.527 |
| 2 cycles | 18(46.15%) | 8 | 10 | |
| 3 and 4 cycles | 21(53.85%) | 12 | 9 | |
| Chemotherapy regimen | | | | 0.741 |
| Docetaxel/cisplatin | 26(66.67%) | 14 | 12 | |
| Docetaxel/carboplatin | 13(33.33%) | 6 | 7 | |

Abbreviations: *N* number; *KPS* Karnofsky Performance Status.
[a] HALP was calculated with hemoglobin, albumin, lymphocyte and platelet values obtained from complete blood cell count and biochemistry evaluation; the blood samples were collected within 3 days before the start of chemoradiotherapy.

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