Research Article

A Novel Inflammation-Based Stage (I Stage) in Patients with Resectable Esophageal Squamous Cell Carcinoma

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Received 23 February 2016; Accepted 29 March 2016

Academic Editor: Czar L. Gaston

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Background. Inflammation plays a key role in cancer. In the current study, we proposed a novel inflammation-based stage, named I stage, for patients with resectable esophageal squamous cell carcinoma (ESCC).

Methods. Three hundred and twenty-three patients with resectable ESCC were enrolled in the current study. The I stage was calculated as follows: patients with high levels of C-reactive protein (CRP) (>10 mg/L), neutrophil-to-lymphocyte ratio (NLR) (>3.5), and platelet-count-to-lymphocyte ratio (PLR) (>150) were defined as I3. Patients with two, one, or no abnormal value were defined as I2, I1, or I0, respectively. The prognostic factors were evaluated by univariate and multivariate analyses.

Results. There were 112 patients for I0, 97 patients for I1, 66 patients for I2, and 48 patients for I3, respectively. The 5-year cancer-specific survival (CSS) in patients with I0, I1, I2, and I3 was 50.0%, 30.9%, 18.2%, and 8.3%, respectively (I0 versus I1, \( P = 0.002 \); I1 versus I2, \( P = 0.012 \); I2 versus I3, \( P = 0.020 \)). Multivariate analyses revealed that I stage was an independent prognostic factor in patients with resectable ESCC (\( P < 0.001 \)). Conclusion. The inflammation-based stage (I stage) is a novel and useful predictive factor for CSS in patients with resectable ESCC.

1. Introduction

The cancer incidence and mortality have been increasing worldwide. Esophageal cancer (EC) is one of the most common cancers and remains the 4th leading cause of cancer death [1]. There are two major histologic types of EC: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). ESCC is the most common pathological type in China [2, 3]. However, the prognosis for patients with ESCC is still poor [3]. Therefore, assessing the prognostic factors in ESCC patients will become more and more important.

Recent reports revealed that inflammation plays an important role in cancer [4, 5]. Therefore, a series of inflammation-based biomarkers, such as C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), and platelet-count-to-lymphocyte ratio (PLR), have been analysed in various cancers [6–11]. However, the prognostic values of these biomarkers in patients with ESCC remain uncertain [12–17]. In addition, most of these studies only evaluated one or two biomarkers without considering others. In the current study, therefore, we proposed a novel inflammation-based stage, named I stage (combination of CRP, NLR, and PLR), for predicting the prognosis for patients with resectable ESCC.

2. Patients and Methods

A retrospective analysis was conducted for patients with ESCC in our hospital from January 2005 to December 2008. Patients with ESCC were confirmed by histopathology. All patients underwent surgery with curative esophagectomy and standard lymphadenectomy. Patients who had received preoperative therapy were excluded. Patients with any form of acute infection or chronic inflammatory disease were also excluded. At last, 323 patients were enrolled in our study. In the current study, a cancer-specific survival (CSS) analysis was ascertained. The last follow-up was on 30 June 2013. This study was approved by the Ethical Committees of Zhejiang Cancer Hospital (Hangzhou, China). All patients were staged according to the 7th edition of the American Joint Committee on Cancer (AJCC) Cancer Staging [18].
TABLE 1: Clinicopathological characteristics for patients with ESCC.

| Case (n, %) | Cases (n, %) |
|-------------|--------------|
| Age (years, mean ± SD) | 59.1 ± 7.9 |
| Gender | 59.1 ± 7.9 |
| Female | 42 (13.0) | | | |
| Male | 281 (87.0) | | | |
| Tumor length (cm, mean ± SD) | 4.3 ± 1.9 |
| Tumor location | 4.3 ± 1.9 |
| Upper | 17 (5.3) |
| Middle | 151 (46.7) |
| Lower | 155 (48.0) |
| Differentiation | 4.3 ± 1.9 |
| Good | 44 (13.6) |
| Moderate | 216 (66.9) |
| Poor | 63 (19.5) |
| T grade | 4.3 ± 1.9 |
| T1 | 55 (17.0) |
| T2 | 55 (17.0) |
| T3 | 179 (55.4) |
| T4 | 34 (10.6) |
| N stage | 4.3 ± 1.9 |
| N0 | 174 (53.9) |
| N1 | 87 (26.9) |
| N2 | 37 (11.5) |
| N3 | 25 (7.7) |
| TNM stage | 4.3 ± 1.9 |
| I | 81 (25.1) |
| II | 104 (32.2) |
| III | 138 (42.7) |
| I stage | 4.3 ± 1.9 |
| I0 | 112 (34.7) |
| I1 | 97 (30.0) |
| I2 | 66 (20.4) |
| I3 | 48 (14.9) |
| CRP (mg/L, mean ± SD) | 9.7 ± 13.5 |
| NLR (mean ± SD) | 3.3 ± 2.8 |
| PLR (mean ± SD) | 160.9 ± 70.6 |

Routine laboratory results (including CRP, neutrophil, lymphocyte, and platelet count) were extracted in retrospective medical records. The definitions of NLR and PLR were described as follows: NLR is neutrophil-to-lymphocyte ratio and PLR is platelet-count-to-lymphocyte ratio. The cut-off values for CRP, NLR, and PLR were 10 mg/L, 3.5, and 150 according to the previous studies [12, 13, 16, 17]. Therefore, the I stage was calculated as follows: patients with high levels of CRP (>10 mg/L), NLR (>3.5), and PLR (>150) were defined as I3. Patients with two, one, or no abnormal value were defined as I2, I1, or I0, respectively.

2.1. Statistical Analysis. The 5-year CSS was analysed by the Kaplan-Meier method. Univariate and multivariate Cox analyses were performed to analyse the prognostic factors.

TABLE 2: The relationship between I stage and clinicopathological characteristics.

| I stage | 0 (n = 112) | 1 (n = 97) | 2 (n = 66) | 3 (n = 48) | P value |
|---------|-------------|------------|------------|------------|---------|
| Age (years) | ≤60 | 66 | 58 | 37 | 25 | 0.817 |
| | >60 | 46 | 39 | 29 | 23 | |
| Gender | Female | 18 | 14 | 5 | 5 | 0.375 |
| | Male | 94 | 83 | 61 | 43 | |
| Tumor length (cm) | ≤3 | 45 | 31 | 9 | 4 | <0.001 |
| | >3 | 67 | 66 | 57 | 44 | |
| Tumor location | Upper | 8 | 4 | 1 | 4 | 0.488 |
| | Middle | 51 | 49 | 28 | 23 | |
| | Lower | 53 | 44 | 37 | 21 | |
| Vessel involvement | Negative | 99 | 79 | 54 | 38 | 0.385 |
| | Positive | 13 | 18 | 12 | 10 | |
| Perineural invasion | Negative | 98 | 70 | 52 | 40 | 0.043 |
| | Positive | 14 | 27 | 14 | 8 | |
| Differentiation | Good | 17 | 10 | 12 | 5 | 0.310 |
| | Moderate | 80 | 65 | 41 | 30 | |
| | Poor | 15 | 22 | 13 | 13 | |
| T stage | T1 | 33 | 18 | 3 | 1 | <0.001 |
| | T2 | 23 | 14 | 11 | 7 | |
| | T3 | 50 | 58 | 42 | 29 | |
| | T4 | 6 | 7 | 10 | 11 | |
| N stage | N0 | 71 | 55 | 32 | 16 | <0.001 |
| | N1 | 30 | 30 | 12 | 15 | |
| | N2 | 6 | 9 | 12 | 10 | |
| | N3 | 5 | 3 | 10 | 7 | |
| TNM stage | I | 46 | 21 | 9 | 5 | <0.001 |
| | II | 31 | 41 | 22 | 10 | |
| | III | 35 | 35 | 35 | 33 | |

Pearson correlation analyses were performed to analyse the correlation. Receiver operating characteristic (ROC) curves were plotted to determine the accuracy of CRP, NLR, and PLR. A P < 0.05 was considered to be statistically significant. Statistical analyses were conducted with SPSS 17.0 (SPSS Inc., Chicago, IL, USA).

3. Results

Clinicopathologic characters were shown in Table 1. The mean CRP, NLR, and PLR were 9.7 ± 13.5 (mg/L), 3.3 ± 2.8, and 160.9 ± 70.6, respectively. The histograms of CRP,
NLR, and PLR were shown in Figure 1. There were significant positive correlations in CRP and NLR ($r = 0.258, P < 0.001$), CRP and PLR ($r = 0.265, P < 0.001$), and NLR and PLR ($r = 0.470, P < 0.001$) (Figure 2). ROC curves for CSS prediction were shown in Figure 3. The area under the curve (AUC) was 0.713 (95% CI: 0.653–0.772, $P < 0.001$) for CRP, 0.650 (95% CI: 0.589–0.711, $P < 0.001$) for NLR, and 0.685 (95% CI: 0.626–0.744, $P < 0.001$) for PLR.

Of the 323 patients, 112 (34.7%) were allocated an I stage 0, 97 (30.0%) were allocated an I stage 1, 66 (20.4%) were allocated an I stage 2, and 48 (14.9%) were allocated an I stage 3, respectively. The relationships between the I stage
and clinicopathological characteristics were shown in Table 2. Our study demonstrated that I stage was associated with tumor length \((P < 0.001)\), perineural invasion \((P = 0.043)\), T stage \((P < 0.001)\), N stage \((P < 0.001)\), and TNM stage \((P < 0.001)\). In addition, our study revealed that CRP, NLR, and PLR were significantly higher in patients with high I stage \((P < 0.001, \text{Figure } 4)\).

The 5-year CSS in patients with I0, I1, I2, and I3 was 50.0%, 30.9%, 18.2%, and 8.3%, respectively \((P < 0.001, \text{Figure } 5)\) (I0 versus I1, \(P = 0.002\); I1 versus I2, \(P = 0.012\);...
Table 3: Univariate analyses for patients with ESCC.

|                        | 5-year CSS (%) | P value | HR (95% CI)       | P value |
|------------------------|----------------|---------|-------------------|---------|
| Age (years)            |                |         |                   |         |
| ≤ 60                   | 30.1           | 0.978   |                   | 0.978   |
| > 60                   | 33.6           |         | 0.996 (0.762–1.302)|         |
| Gender                 |                | 0.322   |                   | 0.327   |
| Female                 | 38.1           |         | 1.000             |         |
| Male                   | 30.6           |         | 1.227 (0.815–1.848)|         |
| Tumor length (cm)      |                | 0.003   |                   | 0.004   |
| ≤ 3                    | 41.6           |         | 1.000             |         |
| > 3                    | 27.8           |         | 1.580 (1.157–2.157)|         |
| Tumor location         |                | 0.556   |                   | 0.564   |
| Upper                  | 41.2           |         | 1.000             |         |
| Middle                 | 33.1           |         | 0.735 (0.385–1.404)| 0.351   |
| Lower                  | 29.0           |         | 0.908 (0.693–1.190)| 0.483   |
| Differentiation        |                | 0.198   |                   | 0.207   |
| Good                   | 38.6           |         | 1.000             |         |
| Moderate               | 31.0           |         | 1.185 (0.786–1.786)| 0.417   |
| Poor                   | 28.6           |         | 1.504 (0.933–2.424)| 0.098   |
| Vessel involvement     |                | 0.007   |                   | 0.008   |
| Negative               | 34.1           |         | 1.000             |         |
| Positive               | 18.9           |         | 1.577 (1.129–2.202)|         |
| Perineural invasion    |                | 0.005   |                   | 0.006   |
| Negative               | 35.0           |         | 1.000             |         |
| Positive               | 17.5           |         | 1.551 (1.135–2.119)|         |
| TNM stage              |                | <0.001  |                   | <0.001  |
| I                      | 51.9           |         | 1.000             |         |
| II                     | 32.7           |         | 1.878 (1.269–2.780)| 0.002   |
| III                    | 18.8           |         | 2.943 (2.039–4.248)| <0.001  |
| I stage                |                | <0.001  |                   | <0.001  |
| I0                     | 50.0           |         | 1.000             |         |
| II                     | 30.9           |         | 1.696 (1.189–2.420)| 0.004   |
| I2                     | 18.2           |         | 2.676 (1.837–3.900)| <0.001  |
| I3                     | 8.3            |         | 4.372 (2.924–6.536)| <0.001  |
| Adjuvant therapy       |                | 0.398   |                   | 0.402   |
| No                     | 32.0           |         | 1.000             |         |
| Yes                    | 30.6           |         | 1.130 (0.849–1.504)|         |
| CRP (mg/L)             |                | <0.001  |                   | <0.001  |
| ≤ 10.0                 | 39.2           |         | 1.000             |         |
| > 10.0                 | 17.1           |         | 2.217 (1.692–2.906)|         |
| NLR                    |                | <0.001  |                   | <0.001  |
| ≤ 3.5                  | 39.0           |         | 1.000             |         |
| > 3.5                  | 17.7           |         | 1.925 (1.471–2.519)|         |
| PLR                    |                | <0.001  |                   | <0.001  |
| ≤ 150                  | 43.9           |         | 1.000             |         |
| > 150                  | 17.3           |         | 2.260 (1.729–2.955)|         |

I2 versus I3, P = 0.020). In addition, our study revealed that patients with CRP (>10.0 mg/L), NLR (>3.5), or PLR (>150) were significantly associated with decreased CSS, respectively (P < 0.001). Then, we further stratified patients into different groups based on TNM stage. Our results demonstrated that I2 versus I3, P = 0.020). In addition, our study revealed that patients with CRP (>10.0 mg/L), NLR (>3.5), or PLR (>150) were significantly associated with decreased CSS, respectively (P < 0.001). Then, we further stratified patients into different groups based on TNM stage. Our results demonstrated that
(Fig. 5). The 5-year CSS in patients with I0, I1, I2, and I3 was 50.0%, 30.9%, 18.2%, and 8.3%, respectively (P < 0.001) (Table 3). In multivariate analyses, we demonstrated that I stage was an independent prognostic factor in patients with resectable ESCC (P < 0.001) (Table 4).

4. Discussion

In the current study, we initially proposed a novel inflammation-based prognostic system, named I stage (combination of CRP, NLR, and PLR), in patients with resectable ESCC. Our study revealed that I stage was associated with tumor length, perineural invasion, and TNM stage. In multivariate analyses, we revealed that I stage is a useful predictor of postoperative CSS in patients with resectable ESCC (P < 0.001). It may well be that the influence of I stage on the subgroup with TNM stage is important for the understanding of its role in patients with ESCC. Our results demonstrated that I stage was also significantly correlated with CSS based on TNM stage.

Limitations should be acknowledged. Firstly, our study was a retrospective study. Secondly, we excluded patients with neoadjuvant treatment, which may have influenced the results. Neoadjuvant treatment will inevitably have an impact.
Figure 6: The predictive values of I stage were significant in patients based on TNM stage. TNM I stage ($P = 0.035$, (a)), TNM II stage ($P = 0.028$, (b)), and TNM III stage ($P < 0.001$, (c)).

In summary, there was a significant association between the I stage (combination of CRP, NLR, and PLR) and clinical characteristics. Based on the results of the current study, we believe that I stage is a novel and useful predictive factor for CSS in patients with resectable ESCC.

Competing Interests
The authors have no competing interests to disclose.
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