OncoTargets and Therapy

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ORIGINAL RESEARCH

Sensitivity value of hematological markers in patients receiving chemoradiotherapy for esophageal squamous cell carcinoma

This article was published in the following Dove Press journal:
OncoTargets and Therapy
13 October 2016
Number of times this article has been viewed

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Background: Hematological markers of the systemic inflammatory response (SIR) including the neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and the combination of NLR with PLR (CNP) are associated with prognosis of patients with esophageal squamous cell carcinoma (ESCC). However, their value in predicting the sensitivity to chemoradiotherapy in patients with ESCC is unclear. The aim of this study was to investigate whether these markers can be used as sensitivity predictors for chemoradiotherapy in patients with ESCC.

Patients and methods: A total of 114 patients with newly diagnosed ESCC were retrospectively evaluated. They were treated with curative intent by primary radiotherapy only or concurrent chemoradiotherapy. These patients were grouped for further analysis according to the optimum cutoff values of NLR, PLR, and CNP. A univariate analysis was conducted to compare the ability of each of the hematological markers of SIR and clinicopathological characteristics. Multivariate analysis was performed to identify whether the markers were associated with the sensitivity to chemoradiotherapy. The relationship between clinicopathological characteristics and hematological markers was assessed.

Results: NLR, CNP, T stage, M stage, and clinical stage were significantly associated with the sensitivity to chemoradiotherapy. In multivariate analysis, CNP and clinical stage were the independent risk factors predicting a poorer sensitivity.

Conclusion: This study validated novel, easy-to-use hematological markers and found that CNP, an SIR score, is an independent hematological marker of poor sensitivity to chemoradiotherapy in patients with ESCC. This may help guide the planning of follow-up regimens.

Keywords: hematological markers, systemic inflammatory response, sensitivity to chemoradiotherapy, neutrophil to lymphocyte ratio, platelet to lymphocyte ratio

Introduction

China has the highest esophageal cancer (EC) morbidity and mortality incidences worldwide;[1] according to the data from the national cancer center, ~477,900 patients were diagnosed with EC in 2015, accounting for one-third of global morbidity and 375,000 patients died from the disease, representing 25% of mortality.[2] Overall, Chinese patients account for more than half of those treated for, and surviving, EC on a global scale.[3] Esophageal squamous cell carcinoma (ESCC) is the most common pathological type of EC in China.[4,5] Since specific symptoms are generally lacking until the disease reaches an advanced stage, early clinical diagnosis and treatment of ESCC are limited and average 5-year survival rates are poor, at only 15%.[6] Most patients received primary radiotherapy only, or concurrent chemoradiotherapy, according to the evidence-based medicine guidelines. However, the evidence-based model is derived from statistical

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Dovepress
http://dx.doi.org/10.2147/OTT.S115011

data from groups of patients; thus, according to this model, many patients with the same stage of disease received the same treatment, despite the fact that the effectiveness of treatment varies greatly among individuals. To improve the effectiveness of the treatment of patients with ESCC and avoid excessive treatment, thereby reducing physical, psychological, and economic burdens, and facilitate personalized treatment, it is important to develop biomarkers for response to radiotherapy or concurrent chemoradiotherapy.

Hanahan and Weinberg[7] proposed additional hallmarks of tumors (four to ten), one of which is tumor-promoting inflammation. Subsequently, a large number of studies have been initiated in this research area[8–11] and have confirmed that systemic inflammatory response (SIR) influences immune surveillance and the effectiveness of cancer treatment.[12] Various preoperative hematological markers of SIR, including neutrophil to lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR), which are referred to collectively as combination of NLR with PLR (CNP), and the Glasgow Prognostic Score (GPS), are strongly associated with prognosis of patients with ESCC. Liu et al[13] reported that GPS and PLR are potential prognostic markers for the disease, while Noble et al[14] demonstrated that serum albumin can be used to predict pathological responses to neoadjuvant chemotherapy. Wang et al[15] also observed that patients with elevated C-reactive protein (CRP) and hypoalbuminemia exhibit poorer responses to radiotherapy in a study of patients undergoing radical radiation and chemotherapy. The usefulness of hematological markers of SIR, such as NLR, PLR, and CNP, to predict response to radiotherapy or chemoradiotherapy has been confirmed in a number of malignancies, including breast,[16] head, and neck cancers.[17] To our knowledge, the prognostic performance of these hematological markers has never previously been compared or validated in patients with ESCC. The aim of this study was to investigate whether hematological markers of SIR, including NLR, PLR and CNP, are useful for prediction of the response of patients with ESCC to chemoradiotherapy.

Patients and methods

Patient groups and demographic characteristics

In this retrospective study, we reviewed 114 patients with ESCC who were treated with primary radiotherapy only or concurrent chemoradiotherapy in the Shandong Cancer Hospital affiliated to Shandong University, between 2013 and 2015. Patients diagnosed with ESCC by radiographical or histological criteria were included. Clinicopathological data collected included demographic information (sex, age, and smoking history), parameters of complete blood counts measured before treatment, tumor stage, adjuvant therapies employed, tumor location, and tumor state before and at the end of radiotherapy (pneumobarium double contrast examination of the upper gastrointestinal tract, comprehensive assessment of computed tomography scan). Cases with a history of other adjuvant therapies or inflammatory disease, and those unable to tolerate the side effects of treatment, were excluded. This study complied with the standards of current ethical guidelines and was approved by the Institutional Ethics Committee of Shandong Cancer Hospital. All subjects included in the study reviewed the study protocol and gave written informed consent to participate in the study.

Treatment modalities

Patients were treated with radical radiotherapy only or concurrent chemoradiotherapy. A total dose of up to 60.0 Gy was delivered by standard fractionated radiotherapy in 30 fractions (on work days; 2.0 Gy per fraction; over a 6-week cycle). Concurrent chemotherapy consisted of a daily dose of cisplatin (25 mg/m^2, days 1–3) with Tegafur (40 mg/m^2, days 1–14) for 21 days per cycle, for a total of two cycles.

Blood samples

Hematological markers of SIR were calculated as described in Table 1, in accordance with the previously published literature.[18–21] NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count, and an NLR cutoff value of 3 was used to divide patients into two groups, where ≤ 3 was considered normal and >3 abnormal. PLR was calculated by dividing the absolute platelet count by the absolute lymphocyte count, and cutoff values of 150 and 300 were used to divide patients into three groups. Patients with both normal NLR (≤ 3) and PLR (<150) were allocated a score of 0. Patients with abnormal values for only one of these parameters were allocated a score of 1, while those with abnormal values of both NLR and PLR were given a score of 2.

Therapeutic evaluation

The end point of this study was tumor control after radiotherapy, which was evaluated using RECIST criteria. Complete response (CR) was defined as the disappearance of all evidence of disease and the normalization of tumor markers for at least 2 weeks. Partial response (PR) was defined as $\geq 30\%$ reduction in unidimensional tumor measurements, without the appearance of any new lesions or the progression of any existing lesion. Progressive disease (PD) was defined as any

of the following: 20% increase in the sum of the dimensions of all measurable lesions, appearance of any new lesion, or reappearance of any lesion that had previously disappeared. Stable disease (SD) was defined as a tumor response not fulfilling the criteria for CR, PR, or PD. Patients demonstrating CR or PR after treatment were defined as responders, whereas those exhibiting SD or PD were classified as resistant.

Statistical analyses

All statistical analyses were performed using the Statistical Package for the Social Sciences Software Program version 17.0 (SPSS Inc., Chicago, IL, USA). Variables included hematological markers of SIR (NLR, PLR, and CNP) and clinicopathological characteristics (sex, age, smoking history, tumor site, tumor stage, and adjuvant therapies). Univariate analysis was performed to determine which variables were associated with response to therapy. Variables generating *P*-values ≤0.05 by univariate analysis were subjected to multivariate logistic regression analysis. $P \leq 0.05$ was considered statistically significant.

Results

Patient characteristics

The clinicopathological characteristics and the hematological markers of SIR are shown in Tables 1 and 2, respectively. Relationships between variables and response to chemoradiotherapy are shown in Table 3.

Predictive factors

A total of 114 patients with ESCC were grouped according to the cutoff values for NLR, PLR, and CNP. As shown in Table 2, 76 and 38 patients were classified into the low and high NLR groups, respectively. Based on PLR values, patients were classified into three groups, with 65, 43, and six patients in the low, medium, and high groups, respectively. Similarly, patients were classified into three groups from low to high based on the CNP level, consisting of 53, 35, and 26 patients, respectively. The relationship between the responsiveness of patients with ESCC to treatment and these markers was analyzed, and the results indicated a highly significant relationship between the response to chemoradiotherapy in patients with ESCC and NLR (*P*=0.019) or CNP (*P*=0.016); however, there was no significant relationship between sensitivity to chemoradiotherapy in patients with ESCC and PLR (*P*=0.148; Table 3).

To identify independent predictive factors, univariate logistic analysis was employed to analyze the relationship between the sensitivity to chemoradiotherapy in patients with ESCC and variables, including clinicopathological characteristics and hematological markers of SIR. The results demonstrated that responses to chemoradiotherapy in patients with ESCC were highly associated with T stage (*P*=0.032), M stage (*P*=0.018), clinical stage (*P*=0.009), NLR (*P*=0.019), and CNP (*P*=0.016; Table 3). Next, multivariate logistic regression analysis was performed to further evaluate factors identified as significant by univariate logistic analysis. The results indicated that only clinical stage (*P*=0.006) and CNP (*P*=0.031) were independent risk factors, with odds ratios (OR) of 3.343 (95% CI 1.421–7.868) and 1.872 (95% CI, 1.060–3.306), respectively (Table 4).

Table 1 Hematological markers

Group	Definition
NLR	
Group 1	NLR ≤3
Group 2	NLR >3
PLR	
Group 1	PLR <150
Group 2	PLR: 150–300
Group 3	PLR >300
CNP	
0 score	NLR ≤3 and PLR <150
1 score	NLR ≤3 or PLR <150
2 score	NLR >3 and PLR >150

Abbreviations: NLR, neutrophil to lymphocyte ratio; PLR, platelet lymphocyte ratio; CNP, combination of NLR with PLR.

Table 2 Patient group and demographic characteristics

Factors	Patient, (N=114), n (%)
Age, years (≤60/>60)	34 (29.8)/80 (70.2)
Sex (male/female)	88 (77.2)/26 (22.8)
Smoking (yes/no)	43 (37.3)/71 (62.3)
Tumor site (cervical/upper 1/3/ middle 1/3/lower 1/3)	11 (9.6)/37 (32.5)/46 (40.4)/20 (17.5)
T stage (I/II/III/IV)	2 (1.8)/11 (9.6)/48 (42.1)/53 (46.5)
N stage (0/I/II/III)	17 (15)/72 (63)/19 (17)/6 (5)
M stage (0/I)	81 (71)/33 (29)
Clinical stage (I/II/III/IV)	4 (3.5)/7 (6.1)/74 (64.9)/29 (25.4)
Adjuvant therapies (radiotherapy only/concurrent chemoradiotherapy)	31 (27)/83 (73)
NLR (≤3/>3)	76 (66.7)/38 (33.3)
PLR (<150/150–300/>300)	65 (57.0)/43 (37.7)/6 (5.3)
CNP (0/1/2 score)	53 (46.5)/35 (30.7)/26 (22.8)

Abbreviations: NLR, neutrophil to lymphocyte ratio; PLR, platelet lymphocyte ratio; CNP, combination of NLR with PLR.

Associations between markers and clinicopathological parameters

Subsequently, the correlation between different SIR hematological markers and clinicopathological characteristics

Table 3 Univariate analysis of radiosensitivity in patients with ESCC

Factor	n	Sensitivity	Resistance	Chi-square	*P*-value
Age, years				0.001	0.98
≤60	34	26	8		
>60	80	61	19		
Sex				2.227	0.136
Male	88	70	18		
Female	26	17	9		
Smoking				1.639	0.201
No	43	30	13		
Yes	71	57	14		
Tumor site				0.079	0.778
Cervical, upper 1/3	48	36	12		
Middle 1/3, lower 1/3	66	51	15		
T stage				4.581	0.032
I–III	52	9	61		
IV	53	37	17		
N stage				1.384	0.500
0	17	14	3		
I	72	56	16		
II/III	25	17	8		
M stage				6.342	0.018
0	81	67	14		
I	33	20	13		
Clinical stage				6.738	0.009
I–III	85	70	15		
IV	29	17	12		
Adjuvant therapies				1.732	0.219
Radiotherapy only	31	21	10		
Concurrent chemoradiotherapy	83	66	17		
NLR				5.460	0.019
≤3	76	63	13		
>3	38	24	14		
PLR				3.826	0.148
<150	65	54	11		
150–300	43	29	14		
>300	6	4	2		
CNP				8.287	0.016
0 score	53	46	7		
1 score	35	26	9		
2 score	26	15	11		

Abbreviations: ESCC, esophageal squamous cell carcinoma; NLR, neutrophil to lymphocyte ratio; PLR, platelet lymphocyte ratio; CNP, combination of NLR with PLR.

was analyzed (Table 5). We identified a close relationship between NLR and T stage (P=0.034) and PLR and age (P=0.05); however, there was no correlation between CNP and any clinicopathological characteristics (Table 5).

Table 4 Multivariate analysis of radiosensitivity in patients with ESCC

	B	Wald	*P*-value	Exp (B), OR	Exp (B), 95% CI
Clinical stage	1.207	7.641	0.006	3.343	1.421–7.868
CNP	0.627	4.668	0.031	1.872	1.060–3.306

Notes: Partial regression coefficient; Wald, Wald test.
Abbreviations: OR, odds ratio; ESCC, esophageal squamous cell carcinoma; CNP, combination of NLR with PLR.

Discussion

In the era of precision medicine, identification of tumor markers predicting the response to chemoradiotherapy is particularly important to facilitate individualized treatment of patients with locally advanced ESCC. Relatively specific markers of patient prognosis and tumor recurrence have been identified for other malignancies, including α-fetoprotein for hepatoma, prostate-specific antigen for prostate cancer, and carbohydrate antigen-199 for pancreatic cancer. However, there are currently no specific markers that can be used to predict the response to chemoradiotherapy in patients with ESCC. Some researchers have used whole genome

Table 5 The relationships between inflammation-based markers and clinicopathological characteristics

	NLR		PLR		CNP		
	≤3	>3	<150	≥150	0 score	1 score	2 score
Age, years							
P-value	0.469		0.05		0.110		
≤60/>60	21/55	13/25	14/51	19/30	39/14	27/8	24/12
Sex							
P-value	0.469		0.934		0.110		
Male/female	56/19	31/7	50/15	38/11	39/14	27/8	24/12
Smoking							
P-value	0.684		0.565		0.815		
No/yes	45/31	24/14	42/23	29/20	33/20	23/12	15/11
Tumor site							
P-value	0.590		0.343		0.521		
Site 1/2[a]	46/46	21/15	30/35	18/31	32/21	18/17	17/9
T stage							
P-value	0.034		0.258		0.187		
Stage 1/2[b]	46/30	15/23	38/27	23/26	33/20	15/20	13/13
N stage							
P-value	0.469		0.441		0.683		
Stage 1/2[c]	10/47/19	7/25/6	8/42/15	9/50/10	7/33/13	4/23/8	6/16/4
M stage							
P-value	1		0.835		0.584		
Stage 1/2[d]	54/22	27/11	47/18	34/15	37/16	27/8	17/9
Clinical stage							
P-value	0.910		0.831		0.281		
Stage 1/2[e]	56/19	28/10	49/16	36/13	40/13	25/10	20/6

Notes: [a]Site 1: cervical and upper third; site 2: middle and lower third. [b]Stage 1: I–II, stage 2: IV. [c]Stage 1:0, stage 2: I and stage 3: II/III. [d]Stage 1:0, stage 2:1. [e]Stage 1: I–III, stage 2: IV.

Abbreviations: NLR, neutrophil to lymphocyte ratio; PLR, platelet lymphocyte ratio; CNP, combination of NLR with PLR.

sequencing[22,23] and non-coding RNA technologies[24] to predict sensitivity to chemoradiotherapy in patients with ESCC; however, markers identified by these approaches have not yet been widely applied clinically, as the technologies involved are expensive, complicated, and time consuming. In this study, we used hematological markers of SIR, specifically NLR, PLR, and CNP, which are cheap, simple, and performed using easy to obtain clinical samples. As both radiotherapy and chemotherapy can suppress hematopoiesis in the bone marrow, evaluation of hematological markers during or after radiotherapy or concurrent chemoradiotherapy does not reflect the baseline impact of SIR on clinical outcome in patients with ESCC. Therefore, we evaluated the parameters of complete blood count measured before treatment. To our knowledge, this study is the first to determine the predicted value of hematological markers for prediction of the response to chemoradiotherapy in patients with ESCC. We showed that NLR and CNP were associated with response to chemoradiotherapy in patients with ESCC. In particular, CNP was identified as an independent hematological marker, with a direct negative correlation between CNP score and response to chemoradiotherapy (ie, the higher the CNP score, the lower the response to chemoradiotherapy).

Virchow was the first to propose an important effect of chronic inflammation on tumors by observing leukocytes in malignant tissue specimens in 1863.[25–27] He assumed that inflammation is involved in initiation and development of carcinogenesis. Since that first observation, evidence of inflammatory infiltration associated with tumors, including ESCC, has accumulated.[28] The underlying mechanism of this phenomenon remains largely unknown; however, hematological markers of SIR are associated with the decline of some functional and immunological factors, which are important for patients.

Variations in NLR reflect changes in the relative abundance of neutrophils and lymphocytes. Tumor cells can generate granulocyte colony-stimulating factor, tumor necrosis factor-alpha, interleukin-1 (IL-1), and IL-6, which can influence leukocyte and neutrophil counts in the bloodstream.[29] Moreover, tumor-associated neutrophils (TAN) can promote tumor cell growth and inhibit antitumor immune responses, and neutrophils in the bloodstream can reflect real-time levels of TAN.[30] In contrast, lymphocytes can inhibit, or even kill, tumor cells and have anti-tumor effects through specific and nonspecific tumor immune responses.[31] However, lymphopenia demonstrates that anti-tumor effects are not necessarily

a standard physiological response in cancer. Chua et al[32] suggested that NLR may be a readily available and useful biomarker for monitoring early responses to chemotherapy and prognosis. There are no reports of the use of NLR to predict the response of ESCC to chemoradiotherapy to date. Our study found that the response to chemoradiotherapy in patients with ESCC was much higher, with a statistically significant difference, in the low NLR group than that in the high NLR group. Other studies have found that NLR is of consistent predictive value in advanced ESCC, including patients requiring radiotherapy or concurrent chemoradiotherapy, or those with inoperable disease.[33] In order to confirm these reports, we analyzed the relationship between NLR and clinicopathological characteristics. The results demonstrated that NLR was correlated with T stage (P=0.034), in agreement with previous literature reports.[13,34]

Variations in PLR reflect differences in the relative abundance of platelets and lymphocytes. Tumors can produce thrombopoietin and tumor-associated inflammatory mediators (eg, IL-1, IL-6), which promote the production of platelets, thereby leading to hypercoagulability in the majority of patients.[35] This state promotes cooperation between tissue factor and VDa factor, leading to the formation of thrombin and activation of the blood coagulation cascade, which facilitates the adherence of circulating tumor cells to the lining of blood vessels, and enhances the potential for proliferation and metastasis of malignant cells, by increasing their capacity to break through the basement membrane. However, studies on the mechanism underlying the use of PLR for prediction of responses to chemoradiotherapy in patients with ESCC are rare, and further research is required in this area. Although our study found that the response to chemoradiotherapy in patients with high PLR values was decreased relative to that in patients with low PLR values, the difference was not statistically significant. We believe that PLR may be associated with tumor heterogeneity, although this hypothesis requires further exploration.

Multivariable analysis indicated that no single hematology marker of SIR was independently associated with response to chemoradiotherapy in patients with ESCC; therefore, an inflammation score was applied. Various prognostic scores based on SIR have been described,[36] among which, CNP and GPS are able to predict the prognosis of patients with operable ESCC.[37–39] We were unable to perform a study of GPS because CRP is not included among routine pre-treatment laboratory tests in our hospital. Our study used the CNP score, which combines NLR and PLR. Univariate analysis showed that CNP was associated with the response to chemoradiotherapy in patients with ESCC (P=0.016). In multivariate analysis, CNP was an independent predictive marker (OR, 1.872; P=0.031).

The results of this study provide comprehensive clinical assessment of patients for whom the relevant indicators, including NLR and CNP, are available and facilitate choice of the most appropriate therapeutic plan for each patient, thereby improving overall survival rates, reducing recurrence, improving quality of life, and diminishing economic burden. This improves the individualized therapy for tumor treatment.

The potential limitations of the present study are as follows: this is a retrospective, single-center study and the results cannot, therefore, be extrapolated to the broader population of patients with ESCC, and the cutoff values for hematology markers were set according to the previously published literature.[18–21] Previous studies have used other methods to determine cutoff values (eg, median values);[21] however, those studies also have disadvantages, since different clinical databases contain various cutoff values, and therefore cannot represent the overall situation. Hence, the use of standardized criteria to determine cutoff values is scientifically very important. To date, no research has reported exploration of standardization of cutoff values, and further large-scale studies to confirm that hematology markers of SIR can be used to predict responses to different treatments, such as radiotherapy and chemotherapy, would be of great clinical value.

Conclusion

Our study demonstrates that NLR and CNP are associated with response to chemoradiotherapy in patients with ESCC. In addition, CNP, an inflammation-based prognostic score, is an independent marker of poor response to chemoradiotherapy in patients with ESCC. These markers are readily available, add no additional cost to standard treatment regimens, and would be easy to implement in all types of hospital.

Disclosure

The authors report no conflicts of interest in this work.

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