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Original Article

Comparison of two inflammation-based prognostic scores in patients with thoracic esophageal cancer undergoing chemoradiotherapy

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Abstract: The aim of this study was to compare the prognostic value of the modified Glasgow Prognostic Score (mGPS) and neutrophil/lymphocyte ratio (NLR) in patients with inoperable thoracic esophageal squamous cell carcinoma (ESCC) undergoing chemoradiotherapy. A total of 212 patients undergoing chemoradiotherapy for newly diagnosed ESCC were enrolled. Complete blood counts with differential counts were obtained at the time of the diagnosis. The relationship between mGPS/NLR and other relevant clinicopathologic variables was analyzed. Overall survival (OS) and progression-free survival (PFS) were calculated. Significant prognostic factors were identified using univariate and multivariate analyses. Receiver operating characteristic curves were used to test the prognostic validity of the mGPS and NLR. Increasing values of the mGPS and NLR were associated with more advanced disease. ROC curves verified that the predictive ability of the mGPS was superior to that of the NLR ($P = 0.048$). Tumor location, T classification, M classification and the mGPS were independent prognostic indicators for the OS of patients with ESCC. T classification, M classification, the mGPS and platelet count were independent prognostic indicators for the PFS of patients with ESCC. In conclusion, the mGPS was superior to the NLR for prognostic prediction in patients with thoracic ESCC.

Keywords: Chemoradiotherapy, esophageal cancer, mGPS, neutrophil/lymphocyte ratio, prognostic factor

Introduction

Esophageal cancer (EC) is one of the most life-threatening tumors. It carries a five-year survival of only 17%, and the prognosis of patients who do not undergo resection is even more disappointing [1]. Chemoradiotherapy is the mainstay of treatment if the tumor is inoperable. The survival benefit of concurrent chemotherapy in patients with unresectable EC who receive radiotherapy has been demonstrated, but the outcome remains dismal [2]. Therefore, identification of prognostic factors to help select patients for individualized treatment is very important.

There is increasing evidence that the inflammatory response in the tumor microenvironment plays an important part in the development and progression of EC [3-5]. Several prognostic factors reflecting systemic inflammation associated with EC have been studied, including a combination of the serum levels of C-reactive protein (CRP) and albumin within the modified Glasgow Prognostic Score (mGPS) and the neutrophil/lymphocyte ratio (NLR) [6, 7]. The NLR and mGPS could be useful markers because they are readily accessible, are based upon quite simple concepts, and inexpensive. In our previous study, we have shown that the mGPS was the independent prognostic factor in patients with unresectable thoracic esophageal squamous cell carcinoma (ESCC) [8]. However, the inflammation-based prognostic marker that is superior for prediction of the prognosis in EC patients is not known.

Table 1. Baseline characteristics of patients (N = 212)

Characteristic	Number of patients
Age (≤ 60/> 60 years)	114/98
Sex (male/female)	166/46
Mean white cell count, $\times 10^9$ (SD)	7.7 (2.5)
Mean neutrophil count, $\times 10^9$ (SD)	4.9 (2.0)
Mean lymphocyte count, $\times 10^9$ (SD)	1.9 (0.75)
Albumin (≥ 35/< 35 g/L)	168/44
C-reactive protein (< 10/≥ 10 mg/L)	90/122
Hemoglobin (≥ 12/< 12 g/dL)	184/28
Plt (≥ 200,000/< 200,000/dL)	163/49
mGPS (0/1/2)	90/78/44
NLR (< 3/≥ 3)	131/81
Location (upper/middle/lower third)	85/104/23
Tumor length (≤ 5/> 5 cm)	112/100
T stage (T1-2/3/4)	37/108/67
N stage (N0/1)	18/194
M stage (M0/1)	103/109
Radiation dose (< 60/≥ 60 Gy)	70/142

SD, standard deviation; *mGPS*, modified Glasgow Prognostic Score; *NLR*, neutrophil/lymphocyte ratio.

The aim of the present study was to determine which prognostic marker (the mGPS or NLR) has greater prognostic value for survival in patients with unresectable thoracic ESCC undergoing chemoradiotherapy.

Materials and methods

Patient characteristics

Between October 2006 and December 2011, the medical records of 212 patients with pathologically proven ESCC diagnosed at Sun Yat-sen University Cancer Center were studied retrospectively. These patients had refused surgery or could not undergo surgery. This study was approved by the institutional review board (IRBs) of Cancer Center, Sun Yat-sen University.

Pretreatment work-up comprised collection of all history-taking, physical examinations, computed tomography of the chest and abdomen, barium esophagography, and endoscopic ultrasonography. We employed the staging system created by the American Joint Committee on Cancer (AJCC; sixth edition). In all patients, the diagnosis was confirmed to be ESCC by pathologic means. The date of last follow-up was April 2013.

Inflammation-based prognostic scores

Complete blood counts with differential counts were obtained at the time of the diagnosis before treatment was initiated. The NLR was calculated from the absolute neutrophil count divided by the absolute lymphocyte count [9]. The mGPS combines values of the serum concentrations of CRP and albumin. Patients who had elevated levels of CRP (> 10 mg/L) and albumin (< 35 g/L) were assigned a score of 2. Patients with only elevated levels of CRP (> 10 mg/L) were assigned a score of 1. Patients with neither of these abnormalities were assigned a score of 0 [10]. No patients showed clinical signs of severe infection at the time of the diagnosis.

Treatment

All patients were treated with conformal radiotherapy using 6-8 MV x-ray, at 1.8-2.0 Gy per fraction five times a week. Patients underwent radiotherapy for 4-6 weeks, receiving a total dose of 47-70 Gy. Computerized imaging was used to define the gross tumor volume (GTV). Local and regional lymph nodes were included in the clinical target volume (CTV). The CTV was defined as having a 3-cm cephalad and caudad margin beyond the GTV. The planning target volume (PTV) was determined by adding 0.8 cm radially to the CTV. Superior and inferior margins were approximately 5 cm beyond the GTV [11].

During the study period, concurrent chemotherapy was administered using regimens that mainly included cisplatin/docetaxel and cisplatin/5-fluorouracil. Eighty-four patients were treated with two cycles of cisplatin (60 mg/m^2 each) administered on days 1 and 29 and 5-fluorouracil (300 mg/m^2/24 h) administered on days 1-3 and days 29-31 [11]. Seventy-eight patients were treated with two cycles of docetaxel (60 mg/m^2 each) and cisplatin (80 mg/m^2 each) delivered on days 1 and 22 of radiotherapy [12]. The remaining 50 patients concurrently received other chemotherapy regimens.

Statistical analyses

The chi-squared test was used to compare categorical variables to ascertain if clinicopathologic data varied with pre-therapy mGPS and NLR. Overall survival (OS) and progression-free

Table 2. Patient characteristics according to the mGPS and NLR

Characteristic	mGPS (number of patients)		*P*	NLR (number of patients)		*P*
	0 (n = 90)	≥ 1 (n = 122)		< 3 (n = 131)	≥ 3 (n = 81)	
Age (≤ 60/> 60 years)	49/41	65/57	0.866	68/63	46/35	0.488
Sex (male/female)	65/25	101/21	0.065	95/36	71/10	0.009
Location (upper/middle/lower)	39/42/9	46/62/14	0.706	46/71/14	39/33/9	0.137
Tumor length (≤ 5/> 5 cm)	58/32	54/68	0.004	80/51	32/49	0.002
T stage (T1-2/3/4)	21/48/21	16/60/46	0.036	29/69/33	8/39/34	0.011
N stage (N0/1)	14/76	4/118	0.002	10/121	8/73	0.569
M stage (M0/1)	56/34	47/75	0.001	68/63	35/46	0.218
Radiation dose (< 60/≥ 60 Gy)	25/65	45/77	0.163	40/91	30/51	0.328
WBC (≤ 9×10^9 L^{-1}/> 9×10^9 L^{-1})	79/11	82/40	0.001	108/23	53/28	0.005
Hemoglobin (≤ 110/> 110 g/L)	3/87	7/115	0.414	4/127	6/75	0.146

MGPS, modified Glasgow Prognostic Score; *NLR*, neutrophil/lymphocyte ratio; *WBC*, white blood cell.

Table 3. Univariate analysis of prognostic factors

Variable	No.	OS	PFS
		P value	*P* value
Age (≤ 60/> 60 years)	114/98	0.363	0.340
Sex (male/female)	166/46	0.959	0.749
Location(upper/middle/lower)	85/104/23	0.014	0.042
Tumor length (≤ 5/> 5 cm)	112/100	0.239	0.073
T stage (T1-2/T3-4)	37/175	0.014	0.014
N stage (N0/N1)	18/194	0.012	0.020
M stage (M0/M1)	103/109	< 0.001	< 0.001
Radiation dose (< 60/≥ 60 Gy)	70/142	0.107	0.150
mGPS (0/1/2)	90/78/44	< 0.001	< 0.001
Albumin (≥ 35/< 35 g/L)	168/44	< 0.001	0.002
CRP (< 10/≥ 10 mg/L)	90/122	< 0.001	0.001
NLR (< 3/≥ 3)	131/81	0.039	0.038
Hemoglobin (≥ 12/< 12 g/dL)	184/28	0.660	0.578
PLT (≥ 200,000/< 200,000/dL)	163/49	0.051	0.019
TB (≤ 1.1/> 1.1 mg/dL)	103/109	0.138	0.131
LDH (≥ 170/< 170 U/L)	105/107	0.085	0.193

MGPS, modified Glasgow Prognostic Score; *NLR*, neutrophil/lymphocyte ratio; *CRP*, C-reactive protein; *PLT*, platelet; *TB*, total bilirubin; *LDH*, lactate dehydrogenase.

survival (PFS) were the study endpoints. OS was calculated from the date of the diagnosis to the date of death or censored at the date of final follow-up. PFS was computed from the date of the diagnosis to the detection of recurrent disease or to the date of death in patients without evidence of disease recurrence, censored at the date of final follow-up. Survival analyses were carried out using the Kaplan-Meier method, and differences between curves analyzed using the log-rank test. Multivariate analyses using the Cox proportional hazards model were used to calculate the hazard ratio (HR) and to test independent significance by backward elimination of non-significant explanatory variables. The criterion for statistical significance was set at $\alpha = 0.05$, and *p* values determined from two-sided tests.

To determine whether one of the independently significant variables was more predictive than the other, the area under the receiver operating characteristic (ROC) curve was calculated using Stata v10 (Stata, College Station, Texas, USA). Remaining statistical analyses were undertaken using SPSS v16.0 (SPSS, Chicago, IL, USA).

Results

Patient characteristics

Table 1 summarizes the demographic and clinical data of the study population. In the whole cohort, there were 166 male (78.3%) and 46 female (21.7%). The median age of patients was 60.0 (range, 37-81) years. The median duration of follow-up for the entire patient group was 17 months (ranging from 3 to 78 months).

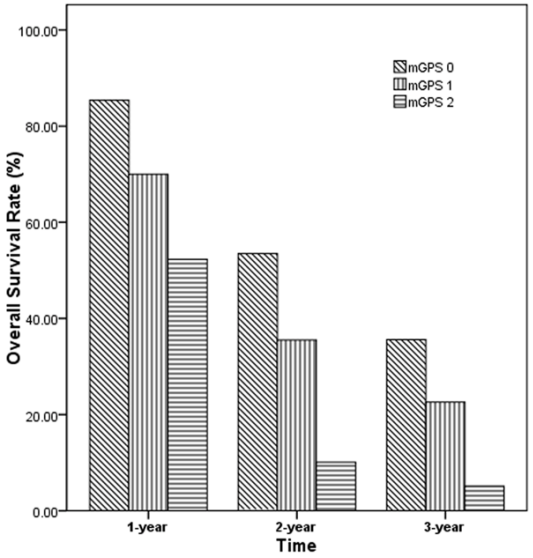

Figure 1. Overall survival according to the mGPS.

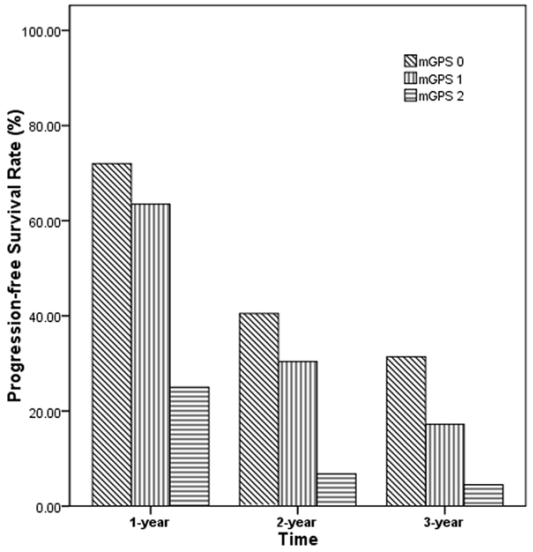

Figure 2. Progression-free survival according to the mGPS.

Correlation of the mGPS and NLR with clinical factors

Table 2 depicts the results of the correlation of the mGPS/NLR with clinicopathologic parameters. An increasing mGPS (mGPS ≥ 1) was significantly associated with higher white blood cell (WBC) count (> 9×10^9 /L), longer tumor length (> 5 cm) and more advanced disease, including advanced T classification, lymph node metastases (N1), distant metastases (M1). The association between mGPS and sex was close to statistical significance ($P = 0.065$). No significant difference in age, tumor location, radiation dose or hemoglobin was found among the mGPS.

The mean neutrophil count was 4.9×10^9/L and the mean lymphocyte count was 1.9×10^9/L. As is shown in **Table 2**, higher NLR (≥ 3) was significantly associated with male patients, higher WBC count (> 9×10^9/L) and more advanced T classification. No significant difference in age, tumor location, N classification, M classification, radiation dose, or hemoglobin level was found among the NLR group.

Prognostic analysis of survival

The 3-year OS of the entire cohort was 24.6% (median: 17.0 months) and the 3-year PFS was 21.3% (median: 14.0 months). The univariate analysis showed that tumor location ($P = 0.014$), T classification ($P = 0.014$), N classification ($P = 0.012$), M classification ($P < 0.001$), the mGPS ($P < 0.001$), albumin level ($P < 0.001$), CRP level ($P < 0.001$) and the NLR ($P = 0.039$) were significantly associated with OS. Variables significantly associated with the PFS were: tumor location ($P = 0.042$), the mGPS ($P < 0.001$), the NLR ($P = 0.038$), T classification ($P = 0.014$), N classification ($P = 0.020$), M classification ($P < 0.001$), albumin level ($P = 0.002$), CRP level ($P = 0.001$) and platelet count ($P = 0.019$) (**Table 3**).

As is shown in **Table 3**, the hypoalbuminemia and higher level of CRP were significantly associated with shorter OS and PFS in the univariate analysis. If these two variables were scored as a combined index (mGPS), the total score demonstrated good stratification for OS and PFS. The 3-year OS for patients with an mGPS of 0, 1 and 2 was 34.6%, 21.7% and 4.5%, respectively (**Figure 1**). The 3-year PFS for patients with an mGPS of 0, 1 and 2 was 29.9%, 16.5% and 0.0%, respectively (**Figure 2**). The increasing mGPS was significantly correlated with a gradual decrease in PFS ($P < 0.001$) and OS ($P < 0.001$).

Median NLR was 2.49 (range, 0.85-16.09). Eighty-one patients (38.2%) had a NLR ≥ 3. Only 16 patients (7.5%) had a NLR ≥ 5. A threshold of NLR = 3 was used. The 3-year OS for patients with a NLR ≥ 3 and NLR < 3 was 27.8% and 17.0%, respectively ($P = 0.039$, **Figure 3**).

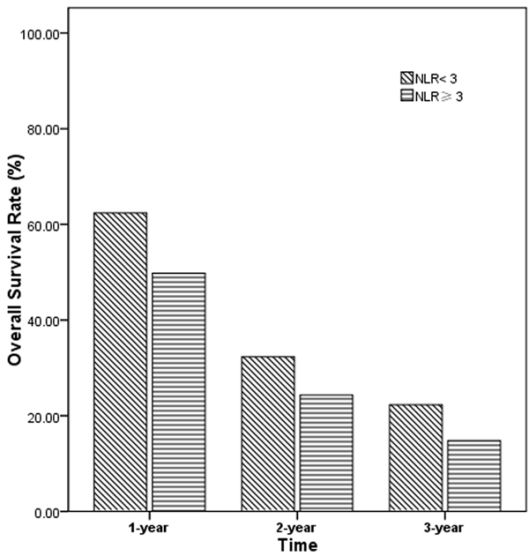

Figure 3. Overall survival according to the NLR.

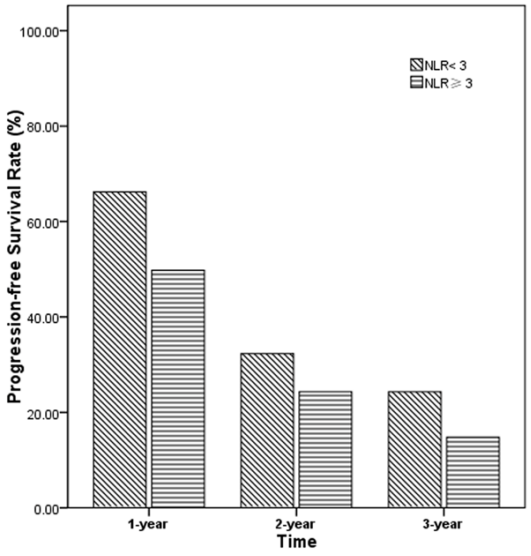

Figure 4. Progression-free survival according to the NLR.

The 3-year PFS for patients with a NLR ≥ 3 and NLR < 3 was 24.3% and 14.8%, respectively (*P* = 0.038, **Figure 4**). An elevated NLR was significantly associated with poorer OS and PFS.

Clinical factors that were statistically significant in a univariate analysis were analyzed further in a multivariate analysis. There was duplication between albumin level, CRP level and the mGPS, so only the latter was entered into the multivariate analysis. Multivariate analysis revealed that tumor location (HR, 1.278; 95% confidence interval [CI]. 1.005-1.625; *P* = 0.045), clinical T classification (HR, 1.269; 1.004-1.604; *P* = 0.046), M classification (HR, 1.571; 1.125-2.195; *P* = 0.008) and mGPS (HR, 1.667; 1.324-2.098; *P* < 0.001) were independent factors affecting OS in patients with ESCC. Clinical T classification (HR, 1.258; 95% CI 1.023-1.571; *P* = 0.045), M classification (HR, 1.796; 1.291-2.490; *P* = 0.001), platelet count (HR, 1.492; 1.014-2.197; *P* = 0.042) and the mGPS (HR, 1.532; 1.220-1.923; *P* < 0.001) were independent factors affecting PFS in ESCC patients (**Table 4**).

Table 4. Multivariate analysis of factors influencing OS and PFS in ESCC

Endpoint	Variable	*P*	HR	95% CI for HR
OS	Location	0.045	1.278	1.005-1.625
	T stage	0.046	1.269	1.004-1.604
	N stage	0.216	1.508	0.786-2.891
	M stage	0.008	1.571	1.125-2.195
	mGPS	< 0.001	1.667	1.324-2.098
	NLR	0.286	1.194	0.862-1.653
PFS	Location	0.381	1.111	0.878-1.404
	T stage	0.045	1.258	1.023-1.571
	N stage	0.264	1.427	0.765-2.664
	M stage	0.001	1.796	1.291-2.490
	mGPS	< 0.001	1.532	1.220-1.923
	Platelet	0.042	1.492	1.014-2.197
	NLR	0.320	1.177	0.854-1.623

MGPS, modified Glasgow Prognostic Score; *NLR*, neutrophil/lymphocyte ratio; *95% CI*, 95% confidence interval; *HR*, hazards ratio; *OS*, overall survival; *PFS*, progression-free survival; *ESCC*, esophageal squamous cell carcinoma.

Prognostic validity of the mGPS and NLR in the study cohort

ROC curves were used to compare the prognostic validity of mGPS and NLR for OS. The area under the curve (AUC) of the mGPS was 0.639 and the standard error (SE) was 0.043. The AUC of the NLR was 0.541 and SE was 0.06. Significance (*P* = 0.048) was observed when comparing these two AUC values (**Figure 5**). The results revealed that, in prediction of the OS of ESCC patients, the mGPS was superior to the NLR.

Discussion

There are very few data on the prognostic role of the mGPS and NLR on the outcome of ESCC patients who cannot undergo resection. This is

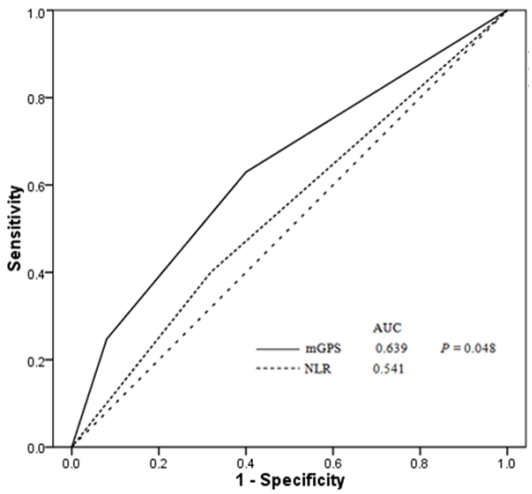

Figure 5. Receiver operator characteristic (ROC) curves for the mGPS and NLR. The *P*-value was compared between the mGPS and NLR.

the first study to compare directly the prognostic value between the mGPS and NLR in patients with unresectable ESCC. Our results showed that the prognostic value of the mGPS was superior to the NLR in patients with inoperable thoracic ESCC undergoing chemoradiotherapy.

It is increasingly recognized that systemic inflammation has an important role in tumor proliferation as well as the survival of EC patients [8, 13, 14]. The mGPS, which is based on a combination of hypoalbuminemia (< 35 g/L) and elevated levels of CRP (> 10 mg/L), is indicative of a nutritional decline and underlying systemic inflammatory response. Vashist et al. reported that the GPS is a strong prognostic factor of perioperative morbidity and long-term outcome in patients with resected esophageal cancer [4]. A higher mGPS was correlated with worse OS and PFS in ESCC patients. Our results could be attributed to the systemic inflammatory response and nutritional decline which the mGPS represents. Firstly, a systemic inflammatory is attributable to an impaired T-lymphocytic response to cancer cells whereas infiltration of $CD8^+$ T cells in EC is a favorable prognostic factor [15]. Secondly, the systemic inflammatory response and accompanying nutritional decline (hypoalbuminemia) reduces patient tolerance to treatment toxicities and diminishes compliance with treatment [16]. Thirdly, elevated CRP levels can accelerate angiogenesis, which is based on increased circulating levels of vascular growth factors and interleukins in patients with gastroesophageal cancer [17, 18].

Studies have shown that the NLR is a poor prognostic marker in individuals with colorectal cancer, lung cancer and malignant lymphoma [19-21]. A high NLR reflects an increased neutrophil and/or a decreased lymphocyte count. A higher NLR is associated with higher levels of LDH, production of which has been attributed primarily to tumor burden [21]. A NLR ≥ 3 was associated with more advanced T stage (P = 0.011). Elevated levels of neutrophils could also form important compartments for circulating vascular endothelial growth factor, and be important for tumor angiogenesis [22]. Also, the NLR has been associated with the systemic inflammatory response [21, 23]. However, whether an elevated NLR is an independent prognostic factor in EC is controversial [22, 24]. Sharaiha et al. reported that an elevated preoperative NLR is associated with significantly worse disease-free survival and OS in EC patients [24]. However, Rashid et al. compared the elevated preoperative NLR in multiple cut-offs and concluded that a high NLR was not a prognostic predictor for EC patients undergoing esophagectomy. They stated that the male predominance for EC may be one of the reasons why the NLR is not an independent prognostic factor [25]. A NLR ≥ 3 was associated with worse OS and PFS in ESCC patients (three-year OS: P = 0.039; three-year PFS: P = 0.038) but in the multivariate analysis, a NLR ≥ 3 was not an independent prognostic factor of OS and PFS.

The AUC of the mGPS and NLR was 0.639 (SE = 0.043) and 0.541 (SE = 0.06). There was significance (P = 0.048) in comparison between these two values of AUC. The results revealed that the mGPS was superior to the NLR for prediction of OS in ESCC patients. Our results were consistent with previous studies. Proctor et al. undertook retrospective analyses of 27,031 patients, and concluded that the mGPS had the greatest AUC when compared with other inflammation-based prognostic scores (including the NLR), which suggested that the mGPS should be included in routine assessment of all patients with cancer [26].

The potential limitations of our study were the nature of a retrospective analysis and the fact that the study was conducted in a single institution. However, we reported on a homogeneous,

large study population that underwent only chemoradiotherapy. Thus, larger prospective studies will need to be carried out to confirm these preliminary results.

Conclusion

The present study showed the prognostic value of the mGPS to be superior to that of the NLR. We suggest that the mGPS could be used in combination with conventional TNM staging to stratify patient for treatment in patients with ESCC undergoing chemoradiotherapy.

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Disclosure of conflict of interest

None.

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