Int J Clin Exp Pathol 2017;10(2):1719-1728
www.ijcep.com /ISSN:1936-2625/IJCEP0045040

Original Article

Prognostic value of pretreatment prognostic nutritional index is superior to neutrophil to lymphocyte ratio for survival in patients with neuroendocrine tumors

Yangwei Fan*, Ke Ma*, Wenxia Niu, Yuan Hu, Enxiao Li, Yinying Wu

*Department of Medical Oncology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, P. R. China. *Equal contributors and co-first authors.*

Received November 24, 2016; Accepted December 28, 2016; Epub February 1, 2017; Published February 15, 2017

Abstract: Purpose: The immune-nutritional factors neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) and prognostic nutritional index (PNI) are prognostic factors for various types of cancer. This study aimed to explore the clinical significance of the immune-nutritional factors in neuroendocrine tumors (NETs). Methods: We retrospectively reviewed patients diagnosed with GEP-NENs or PNETs between January, 2005 and December, 2014 in the First Affiliated Hospital of Xi'an Jiaotong University. The associations between clinicopathological parameters and immune-nutritional factors were assessed via Chi-squared (χ^2) test. The prognostic significance of immune-nutritional biomarkers was determined by both univariate and multivariate Cox survival analysis. Results: In total, 259 patients were enrolled in this study. The pretreatment NLR was significantly associated with distant metastasis and PNI was significantly connected with age, histological grade, TNM stage, lymphatic metastasis and distant metastasis. Univariate analyses showed that overall survival of patients with NETs was significantly associated with histological grade (P<0.001), TNM stage (P<0.001), lymphatic metastasis (P<0.001), distant metastasis (P<0.001), NLR (P<0.001), PLR (P=0.001) and PNI (P<0.001), separately. The Kaplan-Meier survival curves revealed that patients with lower NLR (<2.8), PLR (<142) as well as higher PNI (≥46) had better prognosis. Multivariate analysis exhibited that the NLR (HR, 0.397; 95.0% CI, 0.278-0.568; P<0.001) and PNI (HR, 3.122; 95.0% CI, 2.177-4.478; P<0.001) remained independently associated with the survival time. Subsequent subgroup analysis identified that both lower NLR and higher PNI could predict better prognosis separately in GEP-NEN subgroup and PNET subgroup. Conclusions: Our data suggested that the pretreatment NLR and PLR can be useful prognostic biomarkers for survival in patients with NETs and the PNI was superior to NLR.

Keywords: Neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), prognostic nutritional index (PNI), neuroendocrine tumors (NETs), overall survival (OS), prognosis

Introduction

Neuroendocrine tumors (NETs) are a spectrum of heterogeneous tumors originating from neuroendocrine cells. They can arise in various anatomic sites, but approximately two-thirds of NETs are found in the gastrointestinal tract and one-quarter occur in the bronchopulmonary system. The incidence of NETs has a substantial increase over the last three decades according to recent data from the National Cancer Institute's Surveillance, Epidemiology and End Results database (SEER), possibly related to increased utilization of imaging techniques [1].

According to the revised version of the WHO classification, gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are stratified into two groups: the well-differentiated neuroendocrine tumors (NETs) and the poorly differentiated neuroendocrine carcinomas (NECs) [2]. In addition, pulmonary neuroendocrine tumors (PNETs) are mainly subdivided into two subgroups with four different entities: typical carcinoid (TC) and atypical carcinoid (AC) are well-differentiated neuroendocrine tumors of the lung; however, small cell lung cancer (SCLC) and large cell neuroendocrine carcinoma (LCNEC) are poorly differentiated and highly malignant [3].

Table 1. Baseline characteristics in 259 patients with NETs

Variables	n	%
Gender		
Female	84	32.4
Male	175	67.6
Age		
<60 y	142	54.8
≥60 y	117	45.2
Tumor site		
Stomach	69	26.6
Pancreas	53	20.5
Colon	59	22.8
Lung	78	30.1
Histological grade		
G1/G2	104	40.2
G3	155	59.8
TNM stage		
I/II	83	35.0
III/IV	154	65.0
Lymphatic metastasis		
Yes	132	55.5
No	106	44.5
Distant metastasis		
Yes	95	39.6
No	145	60.4
Functional		
Yes	18	9.9
No	163	90.1
Surgery taken		
Yes	186	71.8
No	73	28.2
CgA expression		
Negative	43	19.8
Positive	174	80.2
Syn expression		
Negative	27	12.6
Positive	187	87.4
NSE expression		
Negative	48	29.1
Positive	117	70.9

Abbreviations: NETs, neuroendocrine tumors; CgA, chromogranin A; Syn, synaptophysin; NSE, neuronspecific enolase.

Increasing evidences prove that effective biomarkers can be helpful in predicting prognosis and guiding surveillance in cancer. Several biomarkers, including programmed death-1 (PD-1) receptor and its ligand programmed death ligand-1 (PD-L1), lactate dehydrogenase (LDH), neuronspecific enolase (NSE), performance status (PS), carcinoembryonic antigen (CEA), plasma sodium, albumin, hemoglobin, and alkaline phosphatase, have been evaluated to better predict prognosis in PNETs [4-9]. However, it's difficult to identify a reliable prognostic indicator owing to conflicting results emerged from independent studies [4, 10]. Thus, new prognostic and predictive markers are urgently needed for patients with PNETs. Meanwhile, the same condition is found in GEP-NETs.

It has increasingly been recognized that the immunological status, consisted of "inflammatory status" and "nutritional condition", is closely related to the survival of patients with various cancers. Inflammation plays a prominent role in tumor progression and metastasis [11]. Inflammatory factors, including neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR), have extensively been studied and found to be independent prognostic factors for colorectal cancer, gastric cancer, pancreatic cancer, non-small cell lung cancer (NSCLC) and SCLC [12-16]. The prognostic nutritional index (PNI), which is calculated on the basis of serum albumin level and total lymphocyte count in peripheral blood, was initially employed to assess the immunological status of patients receiving gastrointestinal surgery [17]. Recent studies also pointed out the prognostic value of PNI in a variety of cancer types including colorectal cancer, gastric cancer, hepatocellular carcinoma and pancreatic cancer [18-21].

To the best of our knowledge, although reported in SCLC, the clinical impacts of immune-nutritional factors have never been investigated in GEP-NETs or in a crowd including all histological types of PNETs. Therefore, in this study, we investigated the correlations of immune-nutritional factors with clinicopathological factors as well as survival data for patients with GEP-NETs or PNETs, as a representative of the whole NETs.

Patients and methods

Patients and samples

We retrospectively reviewed 259 patients (175 males and 84 females aged between 12 and

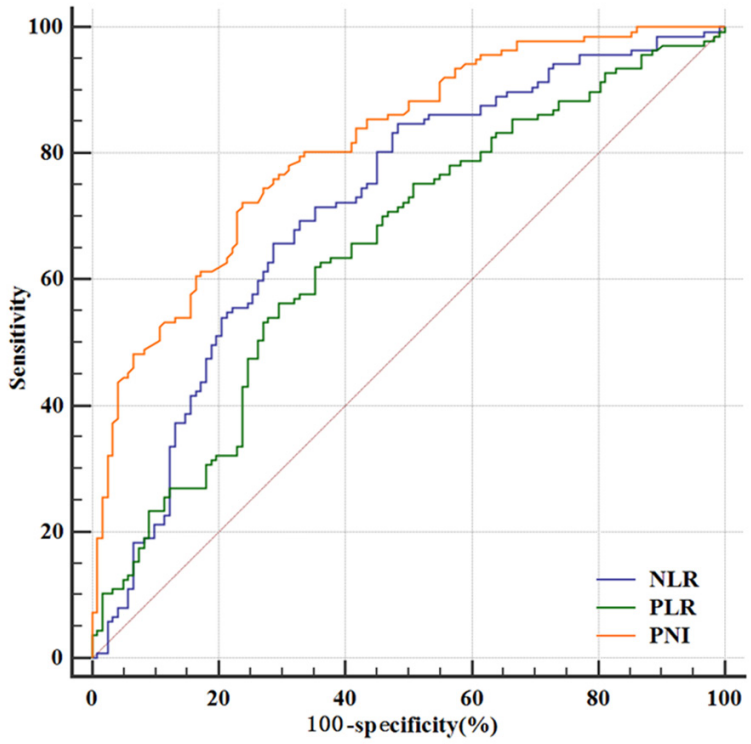

Figure 1. ROC curves for survival prediction. ROC curves were plotted to verify the accuracy of the NLR, PLR and PNI for survival. The AUC was 0.716 for the NLR, 0.650 for the PLR and 0.813 for the PNI, respectively. Thus, the PNI was superior to NLR and PLR as a predictive factor in patients with NETs. Abbreviations: ROC, receiver operating characteristic; AUC, area under the curve; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; PNI, prognostic nutritional index; NETs, neuroendocrine tumors.

84 years) who were histologically diagnosed as GEP-NETs or PNETs between January, 2005 and December, 2014 in the First Affiliated Hospital of Xi'an Jiaotong University. Patients with a prior history of GEP-NETs or PNETs presenting with relapse, prior history of other cancers in preceding 5 years and those with incomplete clinical records or follow-ups were excluded. This study was approved by the Ethics Committees of the First Affiliated Hospital of Xi'an Jiaotong University and all patients signed an informed consent form.

Data collection

We collected patients' clinical characteristics including gender, age, tumor site, histological grade, TNM stage, treatment condition, pathological data, and hematological data. It is worth mentioning that TNM stage was according to the American Joint Committee on Cancer (AJCC; 2010) staging criteria [22].

Immune-nutritional factors were obtained using data from a complete blood count that was routinely performed before treatment. They were separately defined as follows: NLR = peripheral neutrophil count/peripheral lymphocyte count; PLR = peripheral platelet count/peripheral lymphocyte count; and PNI = 10 × serum albumin (g/dL) + 0.005 × total lymphocyte count (per millimeter) [17].

Statistical analysis

SPSS software (Statistical Package for the Social Sciences, version 18.0, SPPS, Inc., Chicago, IL) was used to carry out the statistical analysis. We selected the cut-off values for immune-nutritional factors by using receiver operating characteristic (ROC) curve analysis. The associations between immune-nutritional factors and clinicopathological parameters were assessed via Chi-squared (χ^2) test. Overall survival was defined as the period from the diagnosis day to the end of follow-up. Patients were contacted until the end of the follow-up period (September, 2016) or until death. Survival analysis was performed by Kaplan-Meier plot. We performed multivariate analyses according to the Cox proportional hazards regression model. All statistical tests were two-sided, and $P<0.05$ was considered statistically significant.

Results

Patient characteristics

A total of 259 patients-181 GEP-NENs and 78 PNETs-were enrolled in this study. Particularly worth mentioning is all the included patients came from the Northwest of China, including provinces like Shaanxi, Gansu, Ningxia, Qinghai and Xinjiang and so on. Detailed data on patients' characteristics were presented in **Table 1**.

Table 2. Associations between immune-nutritional factors and clinicopathological characteristics in NETs

Variables	NLR			PLR			PNI		
	<2.8	≥2.8	*P*	<142	≥142	*P*	<46	≥46	*P*
Gender									
Male	85	90	0.451	84	91	0.401	85	90	0.297
Female	45	39		45	39		35	49	
Age									
<60 y	71	71	0.945	72	70	0.750	57	85	0.028[a]
≥60 y	59	58		57	60		63	54	
Histological grade									
G1/G2	58	46	0.142	62	42	0.010[a]	39	65	0.020[a]
G3	72	83		67	88		81	74	
TNM stage									
I/II	46	37	0.171	52	31	0.005[a]	25	58	<0.001[a]
III/IV	71	83		67	87		86	68	
LN metastasis									
Yes	55	51	0.685	59	47	0.183	41	65	0.027[a]
No	65	67		62	70		70	62	
Distant metastasis									
Yes	80	65	0.048[a]	75	70	0.328	55	90	0.001[a]
No	40	55		43	52		57	38	
CgA expression									
Negative	16	27	0.116	20	23	0.586	22	21	0.635
Positive	88	86		89	85		82	92	
Syn expression									
Negative	10	17	0.199	11	16	0.328	12	15	0.607
Positive	94	93		95	92		93	94	
NSE expression									
Negative	27	21	0.328	25	23	0.695	24	24	0.653
Positive	56	61		57	60		54	63	

Abbreviations: NETs, neuroendocrine tumors; LN, lymph node; CgA, chromogranin A; Syn, synaptophysin; NSE, neuronspecific enolase; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; PNI, prognostic nutritional index. a, statistically significant.

Receiver operating characteristic curve for overall survival prediction

The cut-off values of the immune-nutritional factors were decided using receiver operating characteristic (ROC) curve analysis. For the 259 NET patients in our study, an NLR of 2.8 corresponded to the maximum joint sensitivity and specificity on the ROC plot. Thus, the recommended cut-off value for NLR was 2.8. Based on the cut-off value of 2.8, a total of 130 patients (50.2%) were detected with low NLR (<2.8), whereas 129 patients (49.8%) had an NLR of more than or equal to 2.8. With the same method, we separately set 142 and 46 as the cut-offs of PLR and PNI. (**Figure 1**) Besides, the results demonstrated that the area under the curve (AUC) was 0.716 for NLR, 0.650 for PLR and 0.813 for PNI, respectively.

Correlations between clinicopathological parameters and immune-nutritional factors

The mean pretreatment NLR, PLR and PNI were 3.3 (range 0.9 to 24.0), 160 (range 13 to 588) and 46 (range 31 to 65), respectively. The relationships of clinicopathological parameters with the NLR, PLR and PNI were shown in **Table 2**. The pretreatment NLR was significantly associated with distant metastasis (*P*=0.048). The pretreatment PLR was significantly related to histological grade (*P*=0.010) and TNM stage

Table 3. Univariate analysis for the prognosis of patients (n=259) with NETs

Variables	mOS (months)	HR (95% CI)	*P* value
Gender			
Female vs. Male	32.5 vs. 24.8	0.776 (0.538-1.119)	0.173
Age			
<60 y vs. ≥60 y	33.3 vs. 24.8	0.789 (0.563-1.107)	0.168
Histological grade			
G1/G2 vs. G3	67.8 vs. 19.6	0.353 (0.240-0.521)	<0.001[a]
TNM stage			
I/II vs. III/IV	71.8 vs. 17.0	0.282 (0.183-0.432)	<0.001[a]
Lymphatic metastasis			
No vs. yes	67.8 vs. 17.0	0.366 (0.251-0.533)	<0.001[a]
Distant metastasis			
No vs. yes	38.8 vs. 9.3	0.246 (0.172-0.351)	<0.001[a]
CgA expression			
Negative vs. positive	23.9 vs. 26.8	1.061 (0.685-1.642)	0.791
Syn expression			
Negative vs. positive NSE expression	12.5 vs. 26.5	1.306 (0.794-2.148)	0.290
Negative vs. positive	26.8 vs. 33.3	1.160 (0.727-1.850)	0.532
NLR			
<2.8 vs. ≥2.8	42.3 vs. 16.8	0.397 (0.278-0.568)	<0.001[a]
PLR			
<142 vs. ≥142	38.8 vs. 21.5	0.562 (0.397-0.795)	0.001[a]
PNI			
<46 vs. ≥46	16.6 vs. 42.4	3.122 (2.177-4.478)	<0.001[a]

Abbreviations: NETs, neuroendocrine tumors; mOS, median overall survival; HR, hazard ratio; CI, confidence interval; CgA, chromogranin A; Syn, synaptophysin; NSE, neuronspecific enolase; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; PNI, prognostic nutritional index. a, statistically significant.

Table 4. Multivariate analysis to identify factors independently associated with NET prognosis (n=259)

Variables	HR (95% CI)	*P* value
Histological grade		
G1/G2 vs. G3	0.451 (0.286-0.712)	0.001[a]
TNM stage		
I/II vs. III/IV	0.777 (0.459-1.318)	0.350
Lymphatic metastasis		
No vs. yes	0.545 (0.357-0.831)	0.005[a]
Distant metastasis		
No vs. yes	0.387 (0.255-0.588)	<0.001[a]
NLR		
<2.8 vs. ≥2.8	0.528 (0.349-0.798)	0.002[a]
PLR		
<142 vs. ≥142	0.999 (0.664-1.503)	0.994
PNI		
<46 vs. ≥46	1.931 (1.283-2.907)	0.002[a]

Abbreviations: NET, neuroendocrine tumor; HR, hazard ratio; CI, confidence interval; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; PNI, prognostic nutritional index. a, statistically significant.

(*P*=0.005). The pretreatment PNI was significantly connected with age (*P*=0.028), histological grade (*P*=0.020), TNM stage (*P*<0.001), lymphatic metastasis (*P*=0.027) and distant metastasis (*P*=0.001).

Survival analysis for patients with NET using the Kaplan-Meier method and Cox proportional hazards regression model

Univariate analysis showed that overall survival of patients with NET was significantly associated with seven prognostic factors: histological grade (*P*<0.001), TNM stage (*P*<0.001), lymphatic metastasis (*P*<0.001), distant metastasis (*P*<0.001), NLR (*P*<0.001), PLR (*P*=0.001) and PNI (*P*<0.001), separately. (**Table 3**) Subsequently, we subjected significant prognostic factors to multivariate analysis using a Cox proportional hazards model. Multivariate analysis revealed that histological grade (*P*=0.001), lymphatic metastasis (*P*=0.005), distant metastasis (*P*<0.001), NLR (*P*=0.002) and PNI (*P*= 0.002) of NETs remained independently associ-

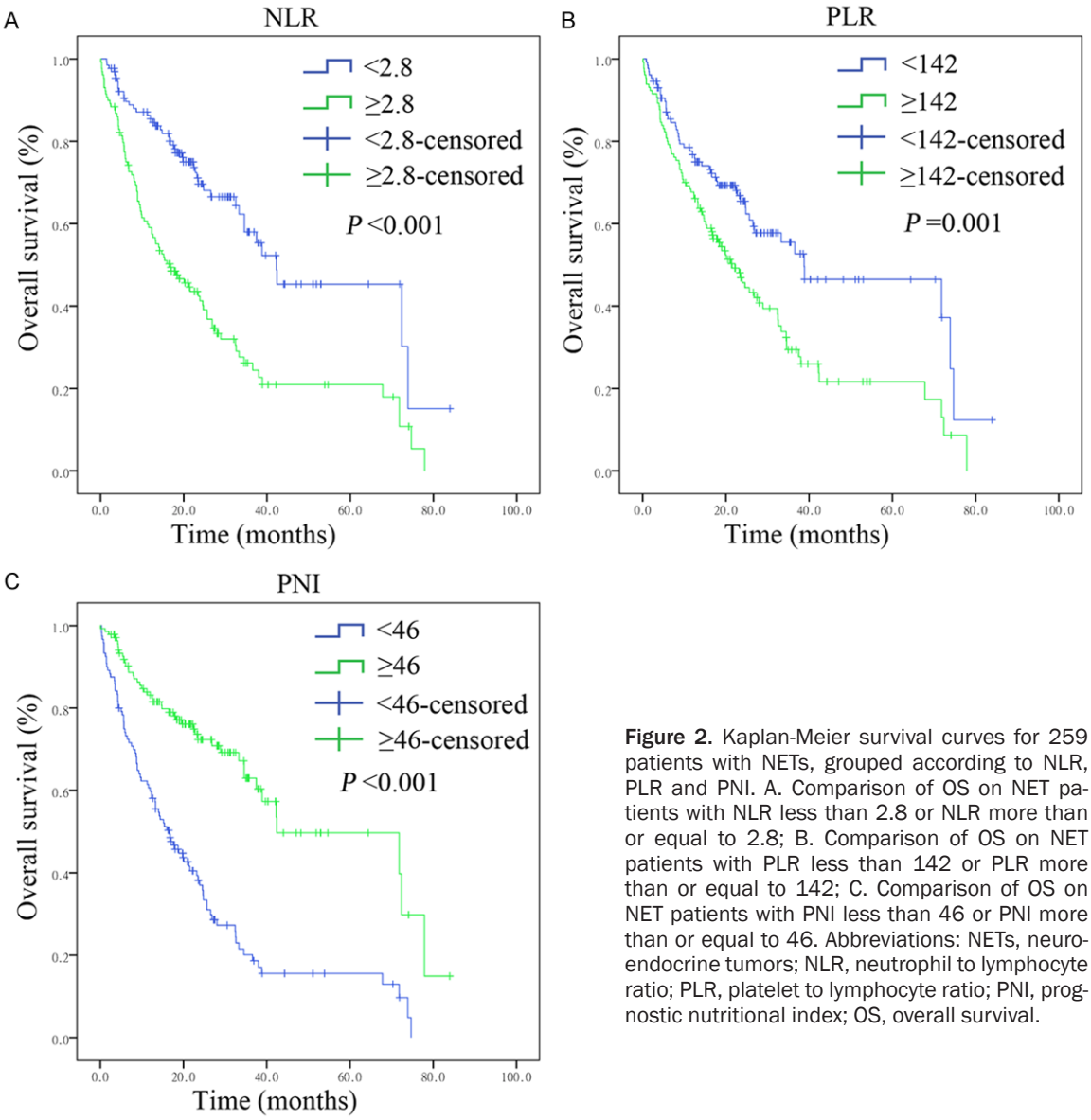

Figure 2. Kaplan-Meier survival curves for 259 patients with NETs, grouped according to NLR, PLR and PNI. A. Comparison of OS on NET patients with NLR less than 2.8 or NLR more than or equal to 2.8; B. Comparison of OS on NET patients with PLR less than 142 or PLR more than or equal to 142; C. Comparison of OS on NET patients with PNI less than 46 or PNI more than or equal to 46. Abbreviations: NETs, neuroendocrine tumors; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; PNI, prognostic nutritional index; OS, overall survival.

ated with the survival time. (**Table 4**) Obviously, the NLR and PNI could be useful prognostic biomarkers for survival in patients with NETs. Furthermore, the Kaplan-Meier survival curves for the high cases and low cases of the NLR, PLR and PNI were shown in **Figure 2**, which revealed that patients with lower NLR, PLR as well as higher PNI had better prognosis.

Subgroup survival analysis

The patients were stratified into GEP-NEN subgroup and PNET subgroup according to primary tumor sites on the purpose of identifying the predictive effects of the NLR and PNI. The subgroup cut-off values of the immune-nutritional factors were also decided using ROC curve analysis, which were 3.3 for NLR in GEP-NETs, 46 for PNI in GEP-NETs, 2.8 for NLR in PNETs and 49 for PNI in PNETs. We performed survival analysis for the high cases and low cases of the NLR and PNI separately in patients with GEP-NETs and PNETs using the Kaplan-Meier method, which showed that both lower NLR and higher PNI could predict better prognosis in GEP-NET subgroup and PNET subgroup (**Figure 3**).

Discussion

Recent data have suggested that systemic immunological status plays a critical role in the

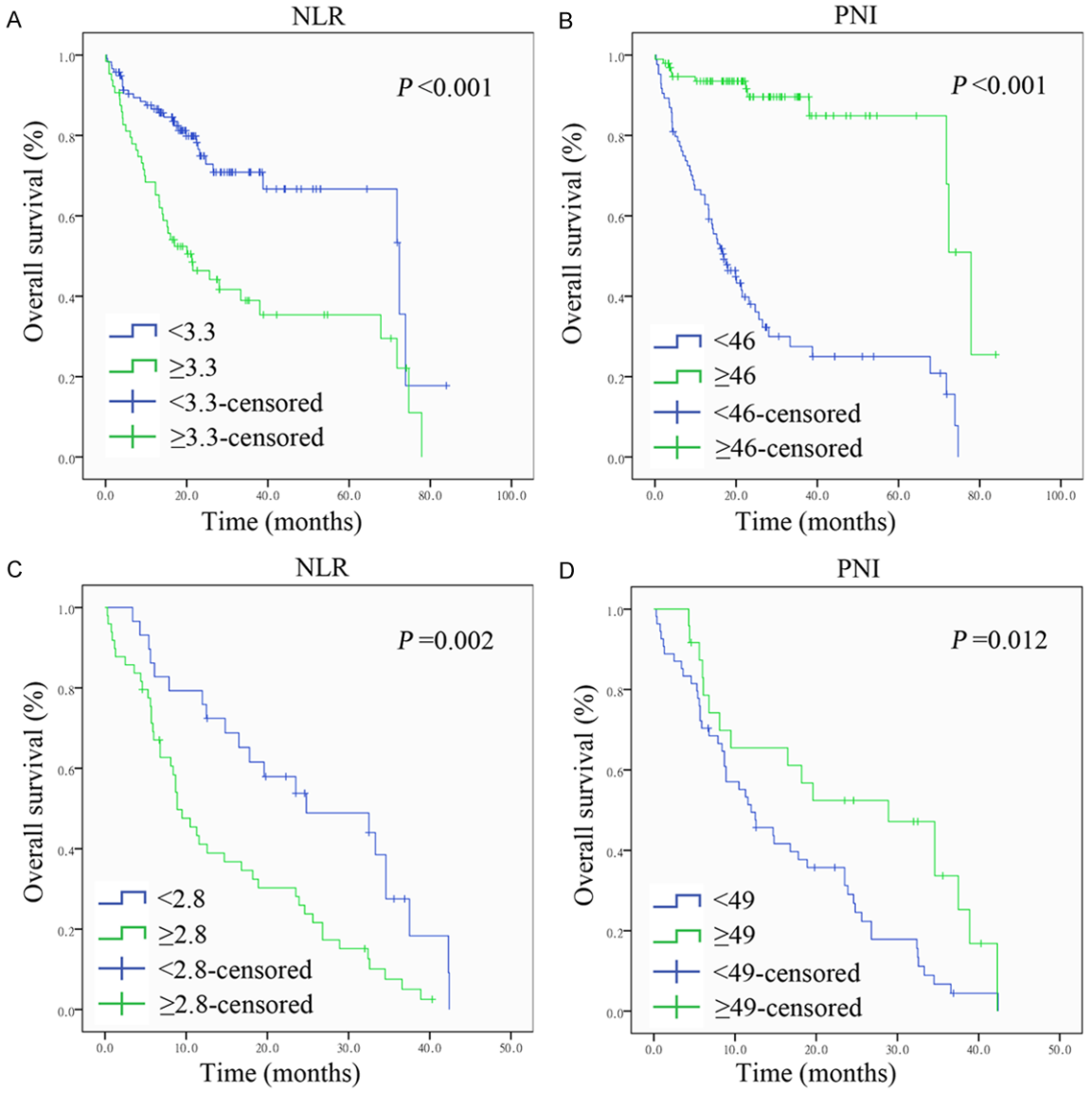

Figure 3. Kaplan-Meier survival curves for 181 patients of GEP-NET subgroup and 78 patients of PNET subgroup. A. Comparison of OS on GEP-NET patients with NLR less than 3.3 or NLR more than or equal to 3.3; B. Comparison of OS on GEP-NET patients with PNI less than 46 or PNI more than or equal to 46; C. Comparison of OS on PNET patients with NLR less than 2.8 or NLR more than or equal to 2.8; D. Comparison of OS on PNET patients with PNI less than 49 or PNI more than or equal to 49. Abbreviations: GEP-NET, gastroenteropancreatic neuroendocrine tumor; PNET, pulmonary neuroendocrine tumor; NLR, neutrophil to lymphocyte ratio; PNI, prognostic nutritional index; OS, overall survival.

development and progression of cancer. Based on peripheral blood cell count and systemic albumin, the NLR, PLR and PNI were initially employed to assess the inflammatory and nutritional status. However, plenty of studies have linked these laboratory immune-nutritional markers to the prognosis of various malignances [12-16, 18-21].

The prognostic values of immune-nutritional factors in certain types of NETs have been investigated. M Kang et al [23] reported the NLR at diagnosis was independent prognostic factor for OS and progression-free survival (PFS) in SCLC. N Shao et al [24] and X Wang et al [25] reported that high pretreatment NLR predicted a poor long-term prognosis for com-

bined small cell lung cancer (C-SCLC), which was defined as a special subgroup of SCLC with many of the features of NSCLC [26]. S Hong et al [27] found that the assessment of the PNI could assist the identification of SCLC patients with poor prognosis. L Cao et al reported that as an independent prognostic factor for gastric neuroendocrine neoplasms (GNENs), blood NLR can improve the predictability of relapse-free survival (RFS) and OS [28].

By contrast, our study owned three improvements. Firstly, our patients came from various provinces of the Northwest of China and we owned a broader sample source. Secondly, various histological types of PNETs including carcinoids, SCLCs, and LCNECs were enrolled in this research. Obviously, we got a more plenary study on PNETs. Finally, it was an integrated retrospective analysis to report the prognostic values of immune-nutritional factors in the systematic NETs.

The cut-off values for the NLR, PLR and PNI were calculated with an ROC curve according to survival prediction in our study. The PNI owned the largest AUC and showed significant difference in pairwise comparison with NLR (P= 0.009) and PLR (P<0.001). Therefore, we could indicate that the PNI was superior to NLR and PLR as a predictive factor in patients with NETs.

Correlations of clinicopathological parameters with the NLR, PLR and PNI were also analyzed. Tumor microenvironment, which is mainly influenced by inflammatory cells, is responsible for carcinogenesis and progression [29-32]. The NLR, PLR and PNI were mainly obtained from the counting of peripheral inflammatory cells. Therefore, it's easy to understand that they were significantly associated with histological grade, TNM stage, lymphatic metastasis or distant metastasis, either of which was recognized as a pivotal prognostic factor in various human tumors. Interestingly, the PNI was significantly connected with age, which may be an accident. Nevertheless, we failed to see other expected clinicopathological associations with the NLR, PLR or PNI. One explanation was that the enrolled number of patients with NETs was too small and insufficient to reach a significant result.

Indeed, univariate analysis in our study revealed that the overall survival time of patients with NETs was significantly associated with the following seven prognostic factors: histological grade, TNM stage, lymphatic metastasis, distant metastasis, the NLR, PLR and PNI, which was more or less different from previous studies. Further, multivariate analysis by a Cox proportional hazards model presented that only the NLR and PNI in NETs remained independently associated with the overall survival time. To identify the predictive effects of NLR and PNI, we carried out a subgroup analysis by tumor sites, which showed that both lower NLR and higher PNI could predict better prognosis separately in GEP-NEN subgroup and PNET subgroup. In all, NLR and PNI can be used as a predictive and prognostic biomarker for patients' survival in NETs and the PNI was superior to NLR.

As a retrospective study, our study was mainly limited by its relatively small number of patients, which might contribute to a conclusion short of generalizability. Therefore, it could be considered as a pilot investigation from which a prospective study could be designed and carried out to verify our finding. Moreover, the cut-off values for the NLR, PLR and PNI were selected based on its prognostic value in our data set, which need to be validated in prospective studies. In addition, although we collected hematological data exclusively within a week before treatment, blood count was unstable and easy to be influenced by various reasons. Nonetheless, this represents the first integrated retrospective study to investigate the prognostic role of immune-nutritional biomarkers in patients with NETs including GEP-NETs and PNETs.

In conclusion, our study searched correlations between immune-nutritional markers with clinicopathological variables and survival time. We confirmed the pretreatment NLR and PNI as the inflammation-based prognostic factors in patients with NETs and the PNI was superior to NLR. Because the assessment of the NLR and PNI is inexpensive and widely available, it could easily assist in predicting prognosis of patients with NETs in routine clinical practice. Data provided by this study pave the way for further validation studies on the prognostic value of immune-nutritional biomarkers.

Acknowledgements

This work was supported by the Natural Science Foundation of China (grant number 81172169).

Disclosure of conflict of interest

None.

Address correspondence to: Drs. Yinying Wu and Enxiao Li, Department of Medical Oncology, The First Affiliated Hospital of Xi'an Jiaotong University, 277 Yanta West Road, Xi'an 710061, Shaanxi, P. R. China. Tel: +86 137 59956366; E-mail: shadowless_111@163.com (YYW); Tel: +86 189 91232168; E-mail: doclienxiao@163.com (EXL)

References

[1] Modlin IM, Lye KD and Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. Cancer 2003; 97: 934-959.

[2] Kloppel G. Classification and pathology of gastroenteropancreatic neuroendocrine neoplasms. Endocr Relat Cancer 2011; 18 Suppl 1: S1-16.

[3] Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JH, Beasley MB, Chirieac LR, Dacic S, Duhig E, Flieder DB, Geisinger K, Hirsch FR, Ishikawa Y, Kerr KM, Noguchi M, Pelosi G, Powell CA, Tsao MS and Wistuba I. The 2015 World Health Organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. J Thorac Oncol 2015; 10: 1243-1260.

[4] Fan Y, Ma K, Wang C, Ning J, Hu Y, Dong D, Dong X, Geng Q, Li E and Wu Y. Prognostic value of PD-L1 and PD-1 expression in pulmonary neuroendocrine tumors. Onco Targets Ther 2016; 9: 6075-6082.

[5] Stokkel MP, van Eck-Smit BL, Zwinderman AH, Willems LN and Pauwels EK. Pretreatment serum lactate dehydrogenase as additional staging parameter in patients with small-cell lung carcinoma. J Cancer Res Clin Oncol 1998; 124: 215-219.

[6] Jorgensen LG, Osterlind K, Genolla J, Gomm SA, Hernandez JR, Johnson PW, Lober J, Splinter TA and Szturmowicz M. Serum neuron-specific enolase (S-NSE) and the prognosis in small-cell lung cancer (SCLC): a combined multivariable analysis on data from nine centres. Br J Cancer 1996; 74: 463-467.

[7] Yang X, Wang D, Yang Z, Qing Y, Zhang Z, Wang G, Yang Z and Wang Z. CEA is an independent prognostic indicator that is associated with reduced survival and liver metastases in SCLC. Cell Biochem Biophys 2011; 59: 113-119.

[8] Maestu I, Pastor M, Gomez-Codina J, Aparicio J, Oltra A, Herranz C, Montalar J, Munarriz B and Reynes G. Pretreatment prognostic factors for survival in small-cell lung cancer: a new prognostic index and validation of three known prognostic indices on 341 patients. Ann Oncol 1997; 8: 547-553.

[9] Laurie SA, Ding K, Whitehead M, Feld R, Murray N, Shepherd FA and Seymour L. The impact of anemia on outcome of chemoradiation for limited small-cell lung cancer: a combined analysis of studies of the National Cancer Institute of Canada Clinical Trials Group. Ann Oncol 2007; 18: 1051-1055.

[10] Schultheis AM, Scheel AH, Ozretic L, George J, Thomas RK, Hagemann T, Zander T, Wolf J and Buettner R. PD-L1 expression in small cell neuroendocrine carcinomas. Eur J Cancer 2015; 51: 421-426.

[11] Mantovani A. Cancer: Inflaming metastasis. Nature 2009; 457: 36-37.

[12] Stotz M, Pichler M, Absenger G, Szkandera J, Arminger F, Schaberl-Moser R, Samonigg H, Stojakovic T and Gerger A. The preoperative lymphocyte to monocyte ratio predicts clinical outcome in patients with stage III colon cancer. Br J Cancer 2014; 110: 435-440.

[13] Lee S, Oh SY, Kim SH, Lee JH, Kim MC, Kim KH and Kim HJ. Prognostic significance of neutrophil lymphocyte ratio and platelet lymphocyte ratio in advanced gastric cancer patients treated with FOLFOX chemotherapy. BMC Cancer 2013; 13: 350.

[14] Smith RA, Bosonnet L, Raraty M, Sutton R, Neoptolemos JP, Campbell F and Ghaneh P. Preoperative platelet-lymphocyte ratio is an independent significant prognostic marker in resected pancreatic ductal adenocarcinoma. Am J Surg 2009; 197: 466-472.

[15] Yao Y, Yuan D, Liu H, Gu X and Song Y. Pretreatment neutrophil to lymphocyte ratio is associated with response to therapy and prognosis of advanced non-small cell lung cancer patients treated with first-line platinum-based chemotherapy. Cancer Immunol Immunother 2013; 62: 471-479.

[16] Hong X, Cui B, Wang M, Yang Z, Wang L and Xu Q. Systemic immune-inflammation index, based on platelet counts and neutrophil-lymphocyte ratio, is useful for predicting prognosis in small cell lung cancer. Tohoku J Exp Med 2015; 236: 297-304.

[17] Onodera T, Goseki N and Kosaki G. [Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients]. Nihon Geka Gakkai Zasshi 1984; 85: 1001-1005.

[18] Ikeya T, Shibutani M, Maeda K, Sugano K, Nagahara H, Ohtani H and Hirakawa K. Maintenance of the nutritional prognostic index predicts survival in patients with unresectable metastatic colorectal cancer. J Cancer Res Clin Oncol 2015; 141: 307-313.

[19] Migita K, Takayama T, Saeki K, Matsumoto S, Wakatsuki K, Enomoto K, Tanaka T, Ito M, Ku-

rumatani N and Nakajima Y. The prognostic nutritional index predicts long-term outcomes of gastric cancer patients independent of tumor stage. Ann Surg Oncol 2013; 20: 2647-2654.

[20] Pinato DJ, North BV and Sharma R. A novel, externally validated inflammation-based prognostic algorithm in hepatocellular carcinoma: the prognostic nutritional index (PNI). Br J Cancer 2012; 106: 1439-1445.

[21] Wang DS, Luo HY, Qiu MZ, Wang ZQ, Zhang DS, Wang FH, Li YH and Xu RH. Comparison of the prognostic values of various inflammation based factors in patients with pancreatic cancer. Med Oncol 2012; 29: 3092-3100.

[22] Edge SB and Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010; 17: 1471-1474.

[23] Kang MH, Go SI, Song HN, Lee A, Kim SH, Kang JH, Jeong BK, Kang KM, Ling H and Lee GW. The prognostic impact of the neutrophil-to-lymphocyte ratio in patients with small-cell lung cancer. Br J Cancer 2014; 111: 452-460.

[24] Shao N and Cai Q. High pretreatment neutrophil-lymphocyte ratio predicts recurrence and poor prognosis for combined small cell lung cancer. Clin Transl Oncol 2015; 17: 772-778.

[25] Wang X, Jiang R and Li K. Prognostic significance of pretreatment laboratory parameters in combined small-cell lung cancer. Cell Biochem Biophys 2014; 69: 633-640.

[26] Babakoohi S, Fu P, Yang M, Linden PA and Dowlati A. Combined SCLC clinical and pathologic characteristics. Clin Lung Cancer 2013; 14: 113-119.

[27] Hong S, Zhou T, Fang W, Xue C, Hu Z, Qin T, Tang Y, Chen Y, Ma Y, Yang Y, Hou X, Huang Y, Zhao H, Zhao Y and Zhang L. The prognostic nutritional index (PNI) predicts overall survival of small-cell lung cancer patients. Tumour Biol 2015; 36: 3389-3397.

[28] Cao LL, Lu J, Lin JX, Zheng CH, Li P, Xie JW, Wang JB, Chen QY, Lin M, Tu RH and Huang CM. A novel predictive model based on preoperative blood neutrophil-to-lymphocyte ratio for survival prognosis in patients with gastric neuroendocrine neoplasms. Oncotarget 2016; 7: 42045-42058.

[29] Kundu JK and Surh YJ. Inflammation: gearing the journey to cancer. Mutat Res 2008; 659: 15-30.

[30] Jackson JR, Seed MP, Kircher CH, Willoughby DA and Winkler JD. The codependence of angiogenesis and chronic inflammation. FASEB J 1997; 11: 457-465.

[31] Mantovani A, Allavena P, Sica A and Balkwill F. Cancer-related inflammation. Nature 2008; 454: 436-444.

[32] Jaiswal M, LaRusso NF, Burgart LJ and Gores GJ. Inflammatory cytokines induce DNA damage and inhibit DNA repair in cholangiocarcinoma cells by a nitric oxide-dependent mechanism. Cancer Res 2000; 60: 184-190.