Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios may aid in identifying patients with non-small cell lung cancer and predicting Tumor-Node-Metastasis stages

FEI XU[1,2*], PENGLIANG XU[3*], WENQIANG CUI[2,4], WEIYI GONG[1,2], YING WEI[1,2], BAOJUN LIU[1,2] and JINGCHENG DONG[1,2]

[1]Department of Integrative Medicine, Huashan Hospital; [2]Institutes of Integrative Medicine; [3]Department of Thoracic Surgery, Huashan Hospital, Fudan University, Shanghai 200040; [4]Department of Integrative Medicine and Neurobiology, State Key Laboratory of Medical Neurobiology, Institute of Acupuncture Research, School of Basic Medical Science, Fudan University, Shanghai 200032, P.R. China

Received June 27, 2017; Accepted February 27, 2018

DOI: 10.3892/ol.2018.8644

Abstract. The present study aimed to identify a high-risk population with non-small cell lung cancer (NSCLC) and to predict TNM stages using the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR). This retrospective study included preoperative data of 171 patients and 105 controls. Compared with healthy controls, patients with NSCLC had higher levels of NLR and PLR (NLR, 2.719±0.183 vs. 1.813±0.079, P<0.01; PLR, 135.800±4.778 vs. 112.000±5.651, P<0.01, respectively). The associations between Tumor-Node-Metastasis stages and the aforementioned parameters were detected (both P<0.01). NLR and PLR improved the rate of early diagnosis of NSCLC, particularly for stages III and IV with a higher area under curve value (0.752 and 0.759, respectively) compared with stage I and II NSCLC. In addition, PLR with a T stage-dependent increase may be a potential and independent predictive marker for T stage (P<0.05); the NLR exhibited an N stage-dependent increase (except for stage N3) and was identified as a marker for N stage (P<0.0001). It was subsequently concluded that NLR and PLR are useful biomarkers in the early diagnosis of NSCLC; that these two parameters were capable of indicating advanced stages, III and IV; and that PLR and NLR were independent predictors for T and N stages, respectively.

Correspondence to: Dr Baojun Liu or Dr Jingcheng Dong, Department of Integrative Medicine, Huashan Hospital, Fudan University, 12 Wu Lu Mu Qi Middle Road, Shanghai 200040, P.R. China
E-mail: lbj825@163.com
E-mail: jcdong2004@126.com

*Contributed equally

Abbreviations: TNM, Tumor-Node-Metastasis; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio

Key words: neutrophil-to-lymphocyte ratio, non-small cell lung cancer, Tumor-Node-Metastasis stages

Introduction

Lung cancer is the leading cause of cancer-associated mortality worldwide, with the highest rate of morbidity and mortality of all cancer types (1). Non-small cell lung cancer (NSCLC) accounts for >80% of newly diagnosed patients (2), with an overall 5-year survival rate of ~17% (3). Unfortunately, majority of patients with NSCLC are diagnosed at an advanced stage (4), and only 20% of patients have the opportunity to undergo surgical therapy (5). Therefore, early diagnosis is important, and a reliable and inexpensive biomarker is required to identify accurate staging.

For clinicians, the Tumor-Node-Metastasis (TNM) staging system provides reliable guidelines for the routine prognosis prediction and treatment of NSCLC (6). This system characterizes the tumor itself, the regional lymph nodes and potentially metastatic sites. Furthermore, TNM stages provide a standard by which patients are classified into different groups with similar prognoses for each staging category (6). The TNM staging system is capable of improving the prediction of outcomes for patients with cancer, including lung cancer, renal cell carcinoma and colorectal cancer (7-9). In addition to early detection, accurate TNM staging exhibited more significant clinical effects.

It is widely acknowledged that inflammation contributes to the development of numerous types of cancer and inflammation is the seventh hallmark of cancer (10), and systemic inflammatory response is important in tumorigenesis and carcinogenesis. Accumulating evidence has suggested that the neutrophil-to-lymphocyte (NLR) and the platelet-to-lymphocyte ratio (PLR), are potential indicators of systemic inflammation and immune response (11,12). These ratios are easily calculated based on the full blood count and have been recognized as convenient, reliable and inexpensive markers to predict the prognosis, progression, survival, metastasis and regional lymph node invasion of patients with various types

of solid tumors (13-15). Several meta-analyses with large sample sizes have evaluated the prognostic role of preoperative NLR and PLR in different types of cancer, revealing that these two ratios are associated with tumor progression and overall survival (OS), including prostate cancer, esophageal cancer and breast cancer (13,16,17). Although a number of studies have confirmed the role of cancer-related inflammation markers, the majority of studies have focused on prognosis and treatment outcomes (18,19).

Recently, an increasing amount of evidence has demonstrated that systemic inflammation is involved in stages of solid tumor development (20,21). The NLR and PLR, as biomarkers conveying information regarding systematic inflammatory response, are described to be used as valuable predictive parameters for tumor stages (20,22). For example, in papillary thyroid cancer, significant elevation of NLR was correlated with an advanced disease stage (20). However, the association between these two ratios and TNM stages in patients with NSCLC has not been fully elucidated. Therefore, the present study aimed to exclusively investigate whether these two indicators may provide useful information for the early detection of NSCLC and may serve important roles in predicting disease stages.

Materials and methods

Patient selection. This retrospective analysis included data from the hospital records of 171 patients with NSCLC who had undergone surgical treatment at Huashan Hospital, Fudan University (Shanghai, China) between October 2013 and March 2016. This included 104 male patients and 67 female patients, with a mean age of 59.313 and an age range of 33-80 years old. The patient exclusion criteria were as follows: Any sign of inflammatory condition, blood transfusion within 3 months, active bleeding during the preceding 2 months, bleeding diathesis, hyperthyroidism or hypothyroidism, connective tissue diseases, anti-coagulant therapy or anti-inflammatory treatment during the preceding week, or receipt of any cancer-specific pretreatment.

The data of healthy controls were obtained from the Physical Examination Center of Huashan, Fudan University. Annual health examinations were performed at the hospital. The exclusion criteria were as described earlier. Additionally, participants with any other diseases or conditions that may confound the interpretation of data (e.g., cancer, immune diseases or pregnancy) were not recruited.

The present study was approved by the Ethics Committee of Huashan Hospital, Fudan University. Written informed consent was obtained from every participant according to the institutional guidelines of Huashan Hospital, Fudan University when they were enrolled.

Data collection and calculation. The records of patients were collected when they first attended the hospital, including identification number, name, age, sex, and TNM stages (according to the seventh edition of the American Joint Committee on Cancer guidelines), and blood counts were routinely measured on the first day the patients were hospitalized. The data of the healthy controls were collected from online medical reports. Next, the NLR ratio was calculated as ratio of the absolute neutrophil number and the absolute lymphocyte number per microliter of whole blood; and the PLR ratio was calculated as ratio of the absolute platelet number and the absolute lymphocyte number per microliter of whole blood.

Statistical analysis. For comparisons between cancer patients and healthy controls, all data were expressed at as the mean ± standard error of mean or median and maximum/minimum or median and interquartile range (25-75%). Student's t-tests and Mann-Whitney U tests were used to compare normally and not normally distributed variables, respectively. One-way analysis of variance, followed by Bonferroni's post hoc test, was used for the comparison between different stages. Statistical analyses were performed using GraphPad Prism 6 (GraphPad Software, Inc., La Jolla, CA, USA) and SPSS version 19 (IBM Corp., Armonk, NY, USA) software. Receiver operating characteristic (ROC) analyses were used to predict the efficacy of NLR and PLR. The associations between NLR or PLR and TNM stages were evaluated using the Kruskal-Wallis test and a multivariate regression model. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. There were ultimately 171 patients and 105 controls available with complete clinical data who were subsequently enrolled in the present study. Table I demonstrates the patient characteristics. The percentages of patients with different stages of cancer were as follows: 80 (46.78%) with Stage I disease, 24 (14.04%) with Stage II disease, 43 (25.14%) with Stage III disease and 24 (14.04%) with Stage IV disease. According to the T, N and M stages, 23.39% patients exhibited deep tumor infiltration (T stage>2), 38.60% exhibited lymphatic invasion (N stage>0) and distant metastasis was observed in 12.28% of patients (M stage=1).

Comparison of NLR and PLR in patients with NSCLC and healthy controls. As demonstrated in Table I, compared with controls, NSCLC patients had higher white blood cell (WBC), neutrophil and platelet counts (all $P<0.05$), but a lower lymphocyte count ($P<0.05$). Despite this, as demonstrated in Fig. 1 and Table II, there were significant differences in the levels of NLR and PLR between the patient and control groups (NLR, 2.719±0.183 vs. 1.813±0.079, $P<0.01$; PLR, 135.800±4.778 vs. 112.000±5.651, $P<0.01$, respectively). ROC analyses were performed to evaluate the accuracy of NLR and PLR in diagnosing NSCLC. The AUC values for NLR and PLR were 0.633 and 0.639, respectively (Fig. 2). These data suggested that these two markers had certain predictive value for the presence of NSCLC.

Association between NLR or PLR and TNM stages in patients with NSCLC. In patients with NSCLC, there were significant differences among the four stages in NLR and PLR (both $P<0.01$, Fig. 3). Therefore, as demonstrated in Table II and Fig. 3A, a significant increase in the NLR was observed in patients with stage III or IV disease, compared with those with stage I disease (both $P<0.05$). For the PLR values, an increasing trend following the tumor stages was observed (Fig. 3B). In comparison with stage I, there was a significantly higher PLR value in stage II

Table I. Demographic information of patients with non-small cell lung cancer and healthy controls.

Variable	Cancer patients	Controls	P-value
All cases, n	171	105	
Age, mean ± SEM	59.313±0.7335	46.11±0.8590	<0.0001[a]
Sex, n			
Male	104	85	0.0008
Female	67	20	
Smoking history, n			
Yes	48	38	0.1811
No	123	67	
Histology, n			
Adenocarcinoma	116		
Squamous cell carcinoma	45		
Large cell carcinoma	1		
Adenosquamous carcinoma	7		
Pleomorphic carcinoma	2		
TNM stage, n (%)			
I	80 (46.78)		
II	24 (14.04)		
III	43 (25.14)		
IV	24 (14.04)		
T stage, n (%)			
T1	41 (23.99)		
T2	90 (52.63)		
T3	29 (16.96)		
T4	11 (6.43)		
N stage, n (%)			
N0	105 (61.40)		
N1	28 (16.37)		
N2	24 (14.04)		
N3	14 (8.19)		
M stage			
M0	150 (87.72)		
M1	21 (12.28)		
WBC, median (range)	6.370 (2.82-18.31)	5.790 (3.37-9.76)	0.0020[a]
Lymphocyte, median (range)	1.802 (0.508-3.604)	1.989 (0.482-3.639)	0.0278[a]
Neutrophil, median (range)	3.74 (0.790-16.050)	3.259 (1.381-6.127)	0.0020[a]
PLT, median (range)	205 (84-324)	219 (74-520)	0.0088[a]

[a]Comparison was performed using a Student's t-test. All other P-values were obtained using Pearson's χ^2 test. SEM, standard error of the mean; TNM, Tumor-Node-Metastasis; WBC, white blood cell count; PLT, platelet count.

(Fig. 3B, P<0.05). Compared with the control group, the levels of NLR and PLR were significantly raised in patients with stage III or IV disease (all P<0.01; Table II). There was no detectable interaction between stage I or II disease and either of these two markers (all P>0.05; Table II).

Evaluation of the diagnostic efficacy for NLR and PLR. Table II demonstrates that levels of NLR and PLR were higher in the patients with stage III or IV disease, compared with the healthy controls (all P<0.01). In addition, significant increases in NLR and PLR were observed in patients with stage III/IV disease, compared with those with stage I/II disease (NLR, 2.115±0.1207 vs. 3.657±0.4031; P<0.0001; PLR, 123.6±4.961 vs. 154.9±9.025, P=0.0012, respectively; Fig. 4. Notably, ROC analysis revealed AUC values for NLR and PLR at 0.752 and 0.719 (Fig. 5), in identifying patients with advanced-stage (III and IV) NSCLC.

Association between NLR or PLR and independent T, N and M stages in patients with NSCLC. Following the aforementioned results that NLR and PLR are independently associated with

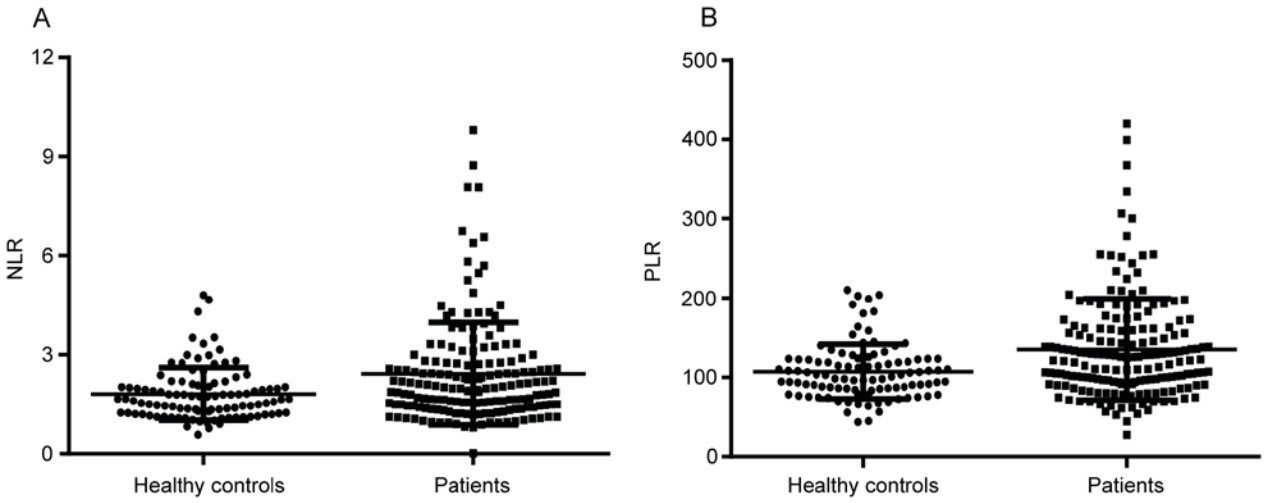

Figure 1. NLR and PLR in patients with NSCLC and healthy controls. Patients with NSCLC had higher preoperative (A) NLR and (B) PLR than healthy controls (both P<0.0001). NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; NSCLC, non-small cell lung cancer.

TNM stages, the present study further investigated whether NLR and PLR are independently associated with T, N or M stages. As demonstrated in Fig. 6A-D, Kruskal-Wallis analysis revealed an association between T stage and increased levels of PLR (P<0.05), and NLR (P<0.0001) and PLR (P<0.05) exhibited an N stage-dependent increase. There was an increasing tendency, but not any significant association, between NLP or PLR and an M stage of M1 (both P>0.05, Fig. 6E and F).

Furthermore, multivariate linear regression (MLR) analyses were employed to evaluate the association between NLR or PLR and T or N stage. MLR detected significant associations between PLR and T stage (P<0.0001), and between NLR and N stage (P<0.0001). However, there was no significant association between PLR and N stage (P=0.768).

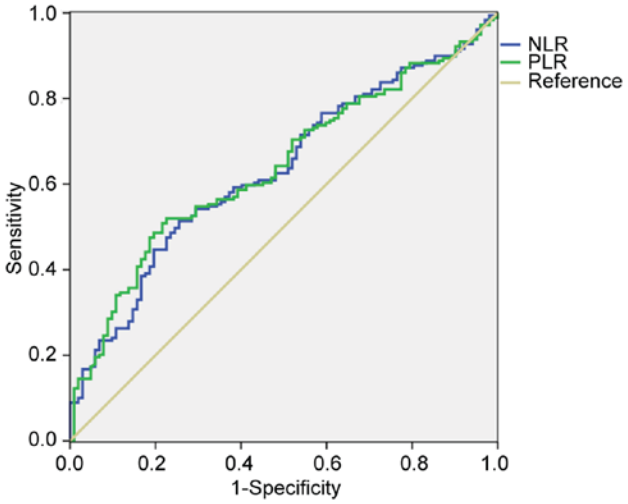

Figure 2. ROC analysis of NLR (blue) and PLR (green) for the occurrence of NSCLC. To discriminate between patients with NSCLC and healthy controls, the AUC values for NLR and PLR obtained from ROC analysis were 0.633 and 0.639, respectively. ROC, receiver operating curve; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; NSCLC, non-small cell lung cancer; AUC, area under the ROC.

Discussion

As stated previously, systemic inflammation serves a critical role in the pathogenesis and progression of cancer (23). As biomarkers of systemic inflammation, NLR and PLR are known to be associated with the progression of different types of cancer (22,24). Notably, previous studies (20-22) have focused on the prognostic role of inflammation. The present study revealed that preoperative levels of NLR and PLR were generally significantly associated with TNM stages. Compared with healthy individuals, patients with NSCLC exhibited higher levels of NLR and PLR. Furthermore, NLR was revealed to be significantly elevated from stage III and IV while PLR was associated with a stage-dependent increase from stage I to stage IV. Additionally, PLR and NLR were independent predictors for T and N stage, respectively. Taken together, the results of the present study indicated that NLR and PLR were involved in different stages of NSCLC and provided important information for advanced disease stages, III and IV.

To the best of our knowledge, the present study was the first to evaluate the association between these two parameters and TNM stages in NSCLC. Accurate staging is not only prognostic, but also helps determine the most appropriate treatment (25,26). To date, TNM stages are determined depending on surgery, pathology, computed tomography (CT) or positron emission tomography (PET)-CT (27,28). At present, great progresses have been made in investigating measures for novel predictive factors, including genetic tests (29). However, they are of high heterogeneity, and are complex and expensive which limits their usage (30). NLR and PLR are fairly simple, convenient and inexpensive as blood parameters for routine clinical monitoring without specialized equipment (31). With regards to NLR and PLR, several published studies have reported that they served reliable roles in predicting and identifying cancer (24,32).

In line with the results of a previous study (32,33), the present study detected that the levels of NLR and PLR were higher in the lung cancer patient group than in the control group, and that NLR and PLR served an important role in the diagnosis of lung cancer. In addition, the results of the present study indicated that these factors were associated with advanced disease stages

Table II. Association between NLR or PLR and TNM stages in lung cancer.

Variable	n (%)	NLR, mean (IQR)	PLR, mean (IQR)
Lung cancer			
TNM stage I	80 (46.78)	1.613 (1.222-2.435)	106.800 (87.480-137.600)
TNM stage II	24 (14.04)	2.170 (1.597-3.294)	110.300 (97.700-168.100)
TNM stage III	43 (25.14)	2.307 (1.636-3.559)[b]	136.100 (93.890-177.600)
TNM stage IV	24 (14.04)	3.108 (1.990-4.285)[b]	139.900 (105.100-196.100)[b]
Total	171 (100)	2.096 (1.466-2.892)	125.100 (93.890-161.700)
Control	105 (100)	1.668 (1.231-2.085)	103.200 (85.250-123.600)
P value		<0.0001[a]	<0.0001[a]

[a]Comparisons were performed using a Student's t-test; P<0.05 compared with controls. [b]Comparisons were performed using analysis of variance; P<0.05, compared with patients with stage I disease. NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; IQR, interquartile range; TNM, Tumor-Node-Metastasis.

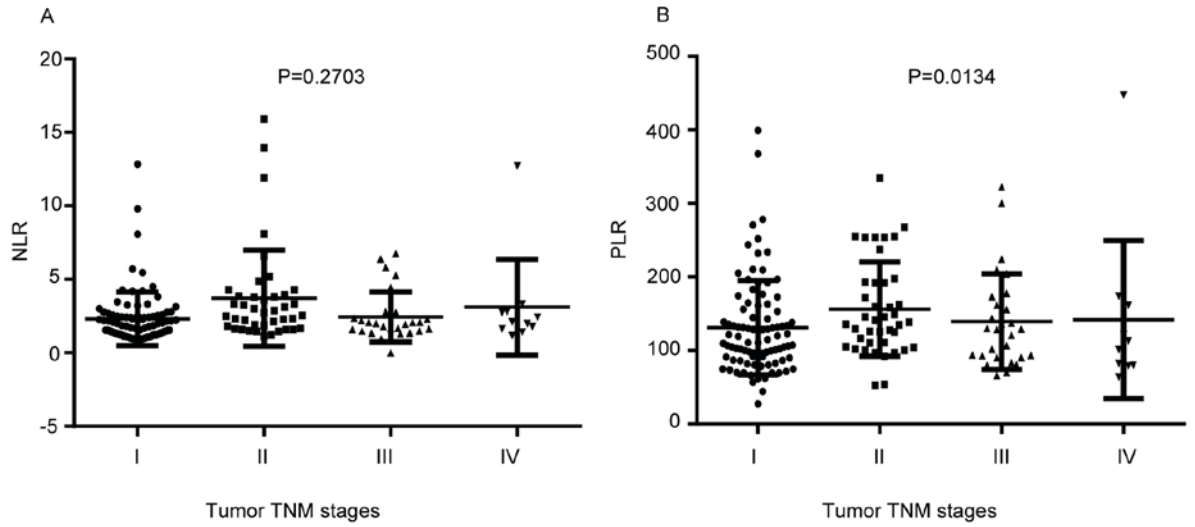

Figure 3. NLR and PLR levels in patients with different TNM stages of disease. (A) There was a significant association between the levels of NLR and TNM stages (P=0.0002). (B) There was a significant association between the levels of PLR and TNM stages (P=0.0055). NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; TNM, Tumor-Node-Metastasis.

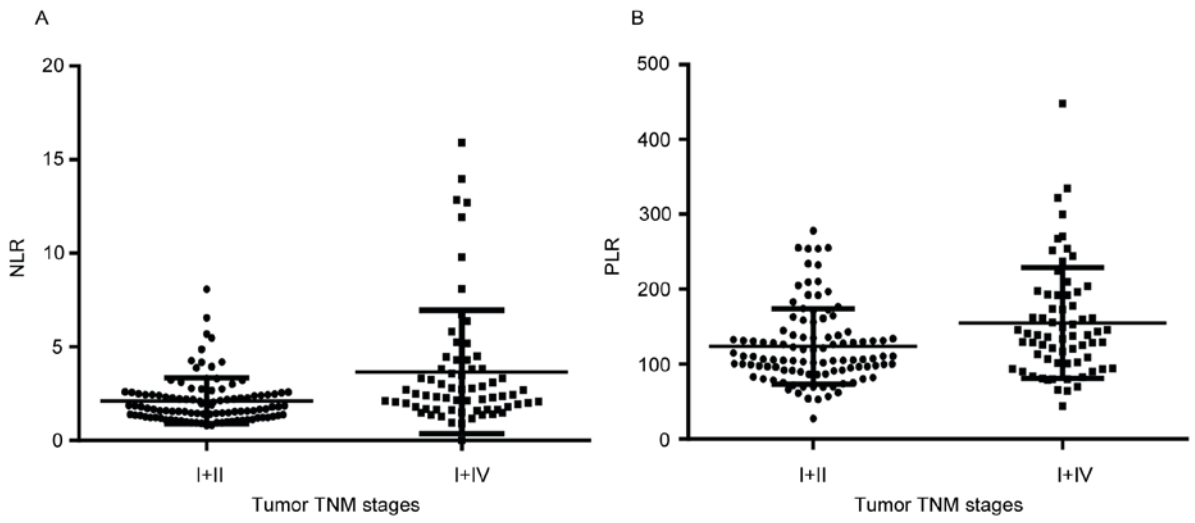

Figure 4. NLR and PLR levels were compared between patients with stage I+II and those with stage III+IV disease. The levels of (A) NLR and (B) PLR in patients' stage III+IV disease were significantly higher than in those with stage I+II disease (P<0.0001 and P=0.0012, respectively). NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; TNM, Tumor-Node-Metastasis.

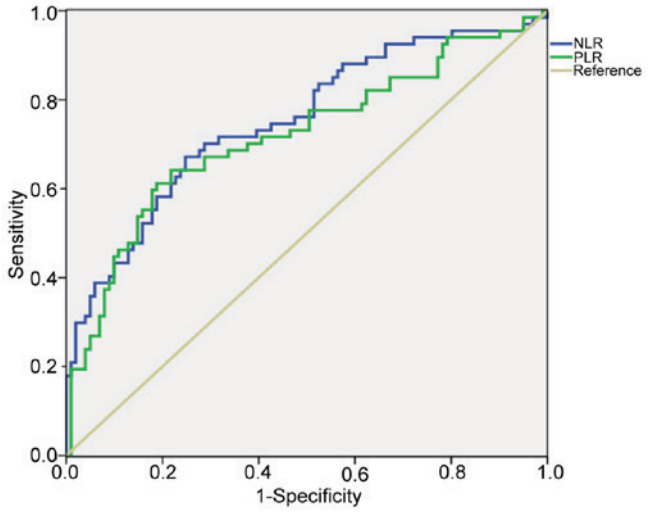

Figure 5. ROC analysis for the NLR (blue) and the PLR (green). ROC analysis revealed a notable AUC value for NLR and PLR at 0.752 and 0.719, respectively, in identifying patients with advanced-stage (III and IV) NSCLC. ROC, receiver operating curve; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; NSCLC, non-small cell lung cancer; AUC, area under the ROC.

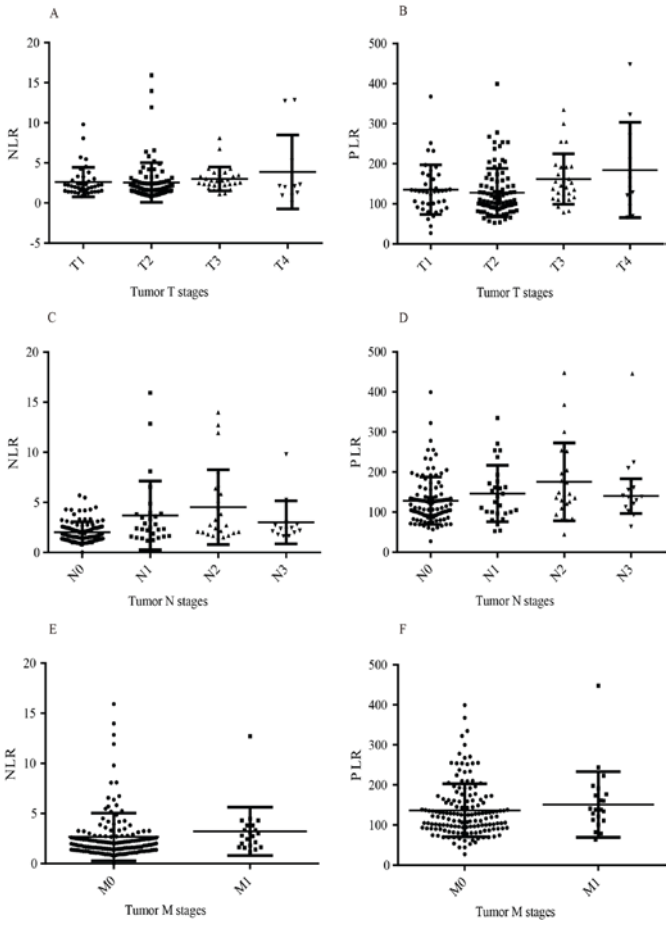

Figure 6. NLR and PLR were compared with T, N and M stages in patients with non-small cell lung cancer. No significant associations were identified between (A) T stage and NLR level (P>0.05); while significant associations were detected between (B) PLR and T stage (P=0.0110). (C) An increased NLR was intrinsically associated with N stage (P<0.0001), with significant differences between N0 and N1 subgroups, and N0 and N2 subgroups (both P<0.001). (D) Significant differences were observed between N stage and PLR (P=0.0185); especially, PLR was higher in the N2 subgroup than in the N0 subgroup (P<0.05). There was no differences were between (E) M stages and NLR levels, or between (F) M stage and PLR (both P>0.05). NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; TNM, Tumor-Node-Metastasis.

(stages III and IV), for which the AUC values were 0.752 and 0.719, respectively, highlighting the precise value of the two markers in the detection of NSCLC, particularly for advanced NSCLC.

Furthermore, growing evidence has suggested an association between inflammatory response and disease stage (20,21,34,35). Elevated preoperative NLR was associated with advanced TNM stage, advanced T stage and lymph node metastasis (20,36). Consistent with previous studies, the results of the present study provided further evidence supporting the notion that NLR and PLR were associated with advanced stages of NSCLC. Notably, the results of the present study expanded on previous findings and revealed that PLR and NLR were independent factors for T and N stage, respectively, in MLR analyses (both P<0.0001), which was in accordance with the results of a recent published study by Jia *et al* (21). Other factors, including NLR and different disease stages of the included patients, may have influenced PLR, as there was no significant difference between PLR and N stage in MLR analysis (P=0.768). In line with the aforementioned results, a high PLR has been revealed to be associated with advanced disease stages (37) and to be a complement of NLR (38).

Neutrophils and lymphocytes are predominant proportions of total circulating leukocytes serving vital roles in the systemic inflammatory response. They may inhibit or promote cancer progression by regulating microenvironment immune interactions. It is more emphasized now that routinely available markers of the systemic inflammatory response, including the NLR and PLR, are associated with tumor length, T stage, cancer development and progression (16,24). Patients with high NLR and PLR have neutrophilia and relative lymphocytopenia, measurable in the peripheral blood (39). It is well known that T-lymphocytes are important components mediating the immune response to cancer cells (40). CD8+ T cells serve a substantial role in inhibiting tumor growth by killing cytotoxic cells and producing cytokine (41). A relative lymphocytopenia is indicative of an immunosuppressive status that inhibits proliferation and metastatic activity of tumor cells (42). By contrast, an increased level of neutrophils represents the host inflammation status, which provides an appropriate environment for tumor growth (43). Numerous lines of evidence have indicated that cancer cells may induce platelet activation and, in turn, that the activated platelets promote cancer cell proliferation, angiogenesis and metastasis and protect tumor cells from apoptosis (44,45). Additionally, platelets are associated with cancer growth and progression (45). NLR and PLR are novel composite inflammatory markers reflecting the immune status of an individual (17,46). Furthermore, it is now indisputable that NLR and PLR provide information regarding the activity of tumor cells, and metastasis and invasion in patients, and that they reflect the degree of cancer progression (22,24,32).

The present study has certain limitations. To begin with, the sample size was relatively small. Additionally, it was a

retrospective and single-center study, with certain bias in recruiting participants. Finally, due to the retrospective nature of the study, it was not possible to control potential factors affecting inflammatory response, including occult infection. Therefore, it is necessary to further investigate the associations between NLR or PLR and the TNM stages of NSCLC in a prospective, large sample, multi-center study.

To conclude, the present study demonstrated that a higher level of NLR and PLR was observed in patients with NSCLC, compared with healthy controls, and that NLR and PLR served vital roles in the early diagnosis of NSCLC, particularly for patients with advanced stages of disease. Therefore, the results of the present study have provided evidence that NLR and PLR were significantly associated with TNM stages in NSCLC. In addition, PLR and NLR may be potential and independent predictive markers for T and N stage, respectively. These observations may provide insight for clinical practice for the diagnosis of NSCLC and for determining an appropriate treatment regimen.

Acknowledgements

The authors would like to thank Dr Zihui Tang for providing statistical guidance.

Funding

The present study was supported by the Natural Science Foundation of China (grant nos. 81673916 and 81403148) and the Development Project of Shanghai Peak Disciplines-Integrative Medicine (grant no. 20150407).

Availability of data and materials.

The data analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

FX, PX, BL and JD conceived and designed the study. FX, WG and YW assisted in data collection and evaluation and analyzed the data. FX and PX wrote the manuscript. BL and JD revised the manuscript and supervised the project.

Ethics statement and consent to participate

The present study was approved by the Ethics Committee of Huashan Hospital, Fudan University. Written informed consent was obtained from every participant according to the institutional guidelines of Huashan Hospital, Fudan University when they were enrolled.

Consent for publication

Written informed consent for publication was obtained from every participant.

Competing interests

The authors declare that they have no competing interests.

References

1. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D and Bray F: GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC cancer base no. 11. Vol. 2016. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. Accessed November 12, 2015.
2. Fossella F, Pereira JR, von Pawel J, Pluzanska A, Gorbounova V, Kaukel E, Mattson KV, Ramlau R, Szczesna A, Fidias P, *et al*: Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: The TAX 326 study group. J Clin Oncol 21: 3016-3024, 2003.
3. Siegel RL, Miller KD and Jemal A: Cancer statistics, 2015. CA Cancer J Clin 65: 5-29, 2015.
4. Mccarthy N: A surprising competitor. Nat Rev Cancer 14: 73, 2014.
5. Park BJ and Rusch VW: Lung cancer workup and staging. In: Sellke FW, del Nido PJ, Swanson SJ, eds. Surgery of the chest, 7th ed. Philadelphia, PA: Elsevier: 241-251, 2005.
6. Andrade FM, Mourad OM and Judice LF: The revised tumor-node-metastasis staging system for lung cancer: Changes and perspectives. J Bras Pneumol 36: 617-620, 2010 (In English, Portuguese).
7. Kucuk U, Pala EE, Sezer O, Cakir E, Bayol U and Divrik RT: Significance of TNM staging, demographic and histologic features in predicting the prognosis of renal cell carcinoma. Acta Chir Belg 115: 202-207, 2015.
8. Costi R, Beggi F, Reggiani V, Riccò M, Crafa P, Bersanelli M, Tartamella F, Violi V, Roncoroni L and Sarli L: Lymph node ratio improves TNM and Astler-Coller's assessment of colorectal cancer prognosis: An analysis of 761 node positive cases. J Gastrointest Surg 18: 1824-1836, 2014.
9. Marquette D, Pichon E, Deschasse G, Lemaire B, Lemarie E, Diot P and Marchand-Adam S: Lung cancer in adults: Better prognosis of patients aged 45 and under related to good condition and lower TNM stage (a comparative and retrospective study). Presse Med 41: e250-e256, 2012 (In French).
10. Mantovani A: Cancer: Inflaming metastasis. Nature 457: 36-37, 2009.
11. Faria SS, Fernandes PJ Jr, Silva MJ, Lima VC, Fontes W, Freitas-Junior R, Eterovic AK and Forget P: The neutrophil-to-lymphocyte ratio: A narrative review. Ecancermedicalscience 10: 702, 2016.
12. Marchioni M, Primiceri G, Ingrosso M, Filograna R, Castellan P, De Francesco P and Schips L: The clinical use of the neutrophil to lymphocyte ratio (NLR) in urothelial cancer: A systematic review. Clin Genitourin Cancer 14: 473-484, 2016.
13. Yodying H, Matsuda A, Miyashita M, Matsumoto S, Sakurazawa N, Yamada M and Uchida E: Prognostic significance of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in oncologic outcomes of esophageal cancer: A systematic review and meta-analysis. Ann Surg Oncol 23: 646-654, 2016.
14. Kim JH, Lee JY, Kim HK, Lee JW, Jung SG, Jung K, Kim SE, Moon W, Park MI and Park SJ: Prognostic significance of the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in patients with stage III and IV colorectal cancer. World J Gastroenterol 23: 505-515, 2017.
15. Sun X, Liu X, Liu J, Chen S, Xu D, Li W, Zhan Y, Li Y, Chen Y and Zhou Z: Preoperative neutrophil-to-lymphocyte ratio plus platelet-to-lymphocyte ratio in predicting survival for patients with stage I-II gastric cancer. Chin J Cancer 35: 57, 2016.
16. Gu X, Gao X, Li X, Qi X, Ma M, Qin S, Yu H, Sun S, Zhou D and Wang W: Prognostic significance of neutrophil-to-lymphocyte ratio in prostate cancer: Evidence from 16,266 patients. Sci Rep 6: 22089, 2016.
17. Templeton AJ, McNamara MG, Šeruga B, Vera-Badillo FE, Aneja P, Ocaña A, Leibowitz-Amit R, Sonpavde G, Knox JJ, Tran B, *et al*: Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: A systematic review and meta-analysis. J Natl Cancer Inst 106: dju124, 2014.
18. Todoric J, Antonucci L and Karin M: Targeting inflammation in cancer prevention and therapy. Cancer Prev Res (Phila) 9: 895-905, 2016.
19. Qi Q, Zhuang L, Shen Y, Geng Y, Yu S, Chen H, Liu L, Meng Z, Wang P and Chen Z: A novel systemic inflammation response index (SIRI) for predicting the survival of patients with pancreatic cancer after chemotherapy. Cancer 122: 2158-2167, 2016.

20. Gong W, Yang S, Yang X and Guo F: Blood preoperative neutrophil-to-lymphocyte ratio is correlated with TNM stage in patients with papillary thyroid cancer. Clinics (Sao Paulo) 71: 311-314, 2016.
21. Jia J, Zheng X, Chen Y, Wang L, Lin L, Ye X, Chen Y, Chen D and Dettke M: Stage-dependent changes of preoperative neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in colorectal cancer. Tumour Biol 36: 9319-9325, 2015.
22. Özgehan G, Kahramanca Ş, Kaya IO, Bilgen K, Bostanci H, Güzel H, Küçükpinar T and Kargici H: Neutrophil-lymphocyte ratio as a predictive factor for tumor staging in colorectal cancer. Turk J Med Sci 44: 365-368, 2014.
23. Shalapour S and Karin M: Immunity, inflammation, and cancer: An eternal fight between good and evil. J Clin Invest 125: 3347-3355, 2015.
24. Bar-Ad V, Palmer J, Li L, Lai Y, Lu B, Myers RE, Ye Z, Axelrod R, Johnson JM, Werner-Wasik M, *et al*: Neutrophil to lymphocyte ratio associated with prognosis of lung cancer. Clin Transl Oncol 19: 711-717, 2017.
25. Wang L, Liang D, Xu X, Jin J, Li S, Tian G, Gao Z, Liu C and He Y: The prognostic value of neutrophil to lymphocyte and platelet to lymphocyte ratios for patients with lung cancer. Oncol Lett 14: 6449-6456, 2017.
26. Marijon H, Bouyon A, Vignot S and Besse B: Prognostic and predictive factors in lung cancer. Bull Cancer 96: 391-404, 2009 (In French).
27. Haberkorn U and Schoenberg SO: Imaging of lung cancer with CT, MRT and PET. Lung Cancer 34 (Suppl 3): S13-S23, 2001.
28. Quint LE: Staging non-small cell lung cancer. Cancer Imaging 7: 148-159, 2007.
29. Foulkes WD, Knoppers BM and Turnbull C: Population genetic testing for cancer susceptibility: Founder mutations to genomes. Nat Rev Clin Oncol 13: 41-54, 2016.
30. Afghahi A and Kurian AW: The changing landscape of genetic testing for inherited breast cancer predisposition. Curr Treat Options Oncol 18: 27, 2017.
31. Semeniuk-Wojtas A, Lubas A, Stec R, Syrylo T, Niemczyk S and Szczylik C: Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and C-reactive protein as new and simple prognostic factors in patients with metastatic renal cell cancer treated with tyrosine kinase inhibitors: A systemic review and meta-analysis. Clin Genitourin Cancer: Feb 2, 2018 (Epub ahead of print).
32. Nikolić I, Kukulj S, Samaržija M, Jeleč V, Žarak M, Orehovec B, Taradi I, Romić D, Kolak T and Patrlj L: Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratio help identify patients with lung cancer, but do not differentiate between lung cancer subtypes. Croat Med J 57: 287-292, 2016.
33. Kemal Y, Yucel I, Ekiz K, Demirag G, Yilmaz B, Teker F and Ozdemir M: Elevated serum neutrophil to lymphocyte and platelet to lymphocyte ratios could be useful in lung cancer diagnosis. Asian Pac J Cancer Prev 15: 2651-2654, 2014.
34. Celik O, Akand M, Keskin MZ, Yoldas M and Ilbey YO: Preoperative neutrophil-to-lymphocyte ratio (NLR) may be predictive of pathologic stage in patients with bladder cancer larger than 3 cm. Eur Rev Med Pharmacol Sci 20: 652-656, 2016.
35. Kim YW, Kim SK, Kim CS, Kim IY, Cho MY and Kim NK: Association of serum and intratumoral cytokine profiles with tumor stage and neutrophil lymphocyte ratio in colorectal cancer. Anticancer Res 34: 3481-3487, 2014.
36. Wang J, Jia Y, Wang N, Zhang X, Tan B, Zhang G and Cheng Y: The clinical significance of tumor-infiltrating neutrophils and neutrophil-to-CD8+ lymphocyte ratio in patients with resectable esophageal squamous cell carcinoma. J Transl Med 12: 7, 2014.
37. Xu Z, Xu W, Cheng H, Shen W, Ying J, Cheng F and Xu W: The prognostic role of the platelet-lymphocytes ratio in gastric cancer: A meta-analysis. PLoS One 11: e163719, 2016.
38. Wu G, Yao Y, Bai C, Zeng J, Shi D, Gu X, Shi X and Song Y: Combination of platelet to lymphocyte ratio and neutrophil to lymphocyte ratio is a useful prognostic factor in advanced non-small cell lung cancer patients. Thorac Cancer 6: 275-287, 2015.
39. Sun H, Hu P, Du J and Wang X: Predictive value of inflammatory indexes on the chemotherapeutic response in patients with unresectable lung cancer: A retrospective study. Oncol Lett 15: 4017-4025, 2018.
40. Chae YK, Galvez C, Anker JF, Iams WT and Bhave M: Cancer immunotherapy in a neglected population: The current use and future of T-cell-mediated checkpoint inhibitors in organ transplant patients. Cancer Treat Rev 63: 116-121, 2018.
41. Durgeau A, Virk Y, Corgnac S and Mami-Chouaib F: Recent advances in targeting CD8 T-Cell immunity for more effective cancer immunotherapy. Front Immunol 9: 14, 2018.
42. Wu ES, Oduyebo T, Cobb LP, Cholakian D, Kong X, Fader AN, Levinson KL, Tanner EJ III, Stone RL, Piotrowski A, *et al*: Lymphopenia and its association with survival in patients with locally advanced cervical cancer. Gynecol Oncol 140: 76-82, 2016.
43. Hwang JE, Kim HN, Kim DE, Choi HJ, Jung SH, Shim HJ, Bae WK, Hwang EC, Cho SH and Chung IJ: Prognostic significance of a systemic inflammatory response in patients receiving first-line palliative chemotherapy for recurred or metastatic gastric cancer. BMC Cancer 11: 489, 2011.
44. van Es N, Sturk A, Middeldorp S and Nieuwland R: Effects of cancer on platelets. Semin Oncol 41: 311-318, 2014.
45. Li N: Platelets in cancer metastasis: To help the 'villain' to do evil. Int J Cancer 138: 2078-2087, 2016.
46. Templeton AJ, Ace O, McNamara MG, Al-Mubarak M, Vera-Badillo FE, Hermanns T, Seruga B, Ocaña A, Tannock IF and Amir E: Prognostic role of platelet to lymphocyte ratio in solid tumors: A systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 23: 1204-1212, 2014.