Clinica Chimica Acta 484 (2018) 272–277

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca

Preoperative increased systemic immune-inflammation index predicts poor prognosis in patients with operable non-small cell lung cancer

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ARTICLE INFO

Keywords:
Systemic immune-inflammation index
Non-small cell lung cancer
Prognosis

ABSTRACT

Background: A novel systemic immune-inflammation index (SII) has been recently reported to be associated with clinical outcome in several tumors. However, the prognostic value of SII has not been reported in operable non-small cell lung carcinoma (NSCLC). We aimed to investigate its clinical and prognostic value in patients with operable NSCLC underwent curative surgery.

Methods: Four hundred ten NSCLC patients staged I-IIIA were included in this retrospective study. The SII was calculated by the formula: neutrophil × platelet/lymphocyte. Receiver operating characteristic (ROC) curve was used to determine the optimal cut-off value for SII. Kaplan-Meier method and Cox proportional regression were used to analyze the prognostic value of SII.

Results: Patients were stratified into high low SII (≤395.4) and SII (> 395.4) groups. High SII was significantly associated with advanced T stage and positive lymph node metastasis. Kaplan-Meier survival analysis showed that SII, PLR, NLR and LMR were all associated with OS. Multivariate analysis identified that SII was an independent predictor of OS. Furthermore, SII remained prognostic significance for NSCLC patients stratified by TNM subgroups.

Conclusions: Preoperative SII was a powerful prognostic biomarker for predicting outcome in patients with operable NSCLC. Preoperative SII may assist clinicians treatment strategy making and individual treatment choice.

1. Introduction

Lung cancer remains the leading cause of cancer death worldwide, non-small cell lung cancer (NSCLC) accounts for > 83% of all cases [1]. In general, for patients with operable NSCLC, radical surgery or combined with neoadjuvant chemotherapy may be the preferred treatment options for cure [2, 3]. Unfortunately, although radical surgery and adequate chemoradiotherapy were done, 6%~40% of patients still have risk of local recurrence and poor prognosis [4]. Currently, prognostic heterogeneity of cancer patients causes confusion among clinicians. Therefore, to identify patients with poor prognosis among the same TNM stage early, more preoperative prognostic prediction biomarkers with are increasingly investigated.

It is known that local immune response and cancer-related inflammation plays an important role in the progress of tumorigenesis, progression, tumor angiogenesis and metastasis [5]. In the clinics, available circulating immune and inflammatory cells mainly included neutrophil (N), lymphocyte (L), monocyte (M) and platelet (P) in peripheral blood. Accordingly, the role of different inflammatory ratios based on the combinations of these cells counts, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR) and monocyte-to-lymphocyte ratio (MLR) are increasingly investigated in progression and prognosis of many malignancies [6–9]. Recently, a novel and integrated systemic immune-inflammation index, SII (SII = N × P/l), based on neutrophil, platelet and lymphocyte counts, was developed and seemed to have a stronger prognostic power [10]. This integrated index, composed of three inflammatory cells, may comprehensively reflect the balance of host immune and inflammatory status. Indeed, the association among the promising index and clinicopathological factors, outcome have been

Abbreviations: SII, Systemic immune-inflammation index, SII = N × P/l; NSCLC, non-small cell lung carcinoma; N, neutrophil; L, lymphocyte; M, monocyte; P, platelet; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; OS, overall survival

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https://doi.org/10.1016/j.cca.2018.05.059
Received 25 February 2018; Received in revised form 6 May 2018; Accepted 29 May 2018
Available online 31 May 2018

Table 1
The relationship between SII and clinicopathological characteristics in NSCLC patients.

Characteristics	Cases	SII ($\times 10^9$/l) mean ± SD	*P* value	Preoperative SII		*P* value
				Low	high	
Sex			0.000			0.000
Male	267	617.6 ± 347.0		71(26.6%)	196(73.4%)	
Female	143	484.8 ± 274.6		69(48.3%)	74(51.7%)	
Age (y)			NS			NS
≤60	199	559.6 ± 291.5		65(32.7%)	134(67.3%)	
>60	211	582.3 ± 361.9		75(35.5%)	136(64.5%)	
Smoking history			NS			NS
None	151	541.4 ± 296.6		57(37.7%)	94(62.3%)	
Yes	259	588.7 ± 346.5		83(32.0%)	176(68.0%)	
Histological type			0.000			0.000
Squamous	191	642.2 ± 354.3		45(23.6%)	146(76.4%)	
Adenocarcinoma	168	473.8 ± 274.2		79(47.0%)	89(53.0%)	
Others	51	626.5 ± 324.5		16(31.4%)	35 (68.6%)	
Tumor location			0.322			0.881
Left	169	552.0 ± 291.2		57(33.7%)	112(66.3%)	
Right	241	584.8 ± 353.7		83(34.4%)	158(65.6%)	
Lesion type			0.001			0.000
Peripheral	289	537.5 ± 336.0		117(40.5%)	172(59.5%)	
Central	121	652.0 ± 299.2		23(19.0%)	98(81.0%)	
T stage			0.000			0.000
T1	139	450.0 ± 249.2		72(51.8%)	67(48.2%)	
T2	232	602.9 ± 345.0		65(28.0%)	167(72.0%)	
T3–4	39	815.5 ± 312.3		3(7.7%)	36(92.3%)	
Lymph node metastasis			NS			0.011
No	237	550.2 ± 341.5		93(39.2%)	144(60.8%)	
Yes	173	600.1 ± 310.7		47(27.2%)	126(72.8%)	
NLR			0.000			0.000
Low	174	351.6 ± 156.5		123(70.7%)	51(29.3%)	
High	236	733.3 ± 329.8		17(7.2%)	219(92.8%)	
PLR			0.000			0.000
Low	148	347.2 ± 136.3		100(67.6%)	48(32.4%)	
High	262	697.9 ± 339.1		40(15.3%)	222(84.7%)	
LMR			0.000			0.000
Low	180	732.6 ± 378.2		30(16.7%)	150(83.3%)	
High	230	445.1 ± 213.4		110(47.8%)	120(52.2%)	

NLR = neutrophil to lymphocyte ratio; PLR = platelet to lymphocyte ratio; LMR = lymphocyte-to-monocyte ratio; SD = standard deviation; SII = immune-inflammation index;

explored in small cell lung cancer [11], esophageal suqamous cell [12] and hepatocellular cancers [10]. However, the prognostic value of SII in operable NSCLC has not been reported to date.

2. Patients and methods

2.1. Study patients

We retrospectively analyzed 410 patients with primary NSCLC who underwent curative resection between January 2009 and December 2011 at Tianjin Medical University Cancer Hospital. Patients who met the following inclusion criteria were included: (a) primary NSCLC confirmed by histopathology; (b) had detailed clinicopathological and follow-up data; (c) stage I to stage IIIA according to the 7th edition of AJCC tumor-node-metastasis (TNM) classification; (d) had measurement of neutrophil, lymphocyte, monocyte and platelet within 1 weeks before surgery. The exclusion criteria: (a) received neoadjuvent chemotherapy or chemoradiotherapy; (b) had chronic inflammatory, autoimmune or hematologic diseases; (c) the use of anti-inflammatory or immunosuppressive medicines. All tumor staging and pathological classification were evaluated according to 7th edition AJCC TNM classification. This study was approved by the Ethics Committee of Tianjin Medical University Cancer Hospital.

2.2. Assessment of SII and other inflammation-based prognostic scores

Preoperative blood samplings before surgery were collected in ethylenediaminetetraacetic acid containing tube. A routine laboratory complete blood count was analyzed by using a standard Coulter counter (Model XE2100; Sysmex Co.). The SII, NLR, PLR and LMR were calculated as follows: SII = N × P/l; PLR = P/l; NLR = N/l; LMR = L/M, where N, L, M, and P refer to peripheral neutrophil, lymphocyte, monocyte and platelet.

2.3. Follow up

Patients were followed up carefully after surgery through patient medical records and telephone interview. Overall survival (OS) was defined as the interval from the date of surgery to the date of death or last follow-up. The last follow-up date was December 2016.

2.4. Statistical analysis

All statistical analyses were performed using SPSS statistical software for Windows, ver 17. The optimal cut-off values for SII, NLR, PLR, and LMR were calculated using the receiver operating characteristics (ROC) curve analysis. Association between categorical variables was assessed using the χ^2 or Fisher's exact test. OS was defined as the interval from the date of surgery to the date of death or last follow-up. Survival analysis was performed using the Kaplan-Meier method and the Log-rank test was used to compare the survival differences. The univariate and multivariate analyses were calculated by the Cox proportional hazards regression model. Comparisons of ROC curves were conducted to compare the ability of different factors in predicting OS. All 2-sided *P*- < 0.05 were considered statistically significant.