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Research Article

The Prognostic Value of Systemic Immune-Inflammation Index in Non-Small Cell Lung Cancer with ALK-Rearrangement

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Abstract

Objectives: EML4-ALK rearrangement is found in a small group of non-small cell lung cancer (NSCLC). In this patient population, the search of the predictive and prognostic biomarkers have been still continuing. Systemic immune-inflammation index (SII) is a novel marker for reflection of the inflammatory condition of the human body. So, we aimed that evaluated the prognostic value of SII in NSCLC with ALK rearrangement.

Methods: The patients who diagnosed advanced NSCLC with ALK rearrangement and received crizotinib at any-line of treatment were enrolled to study. SII was calculated by using formula as follow: (Neutrophil x platelet) / lymphocyte. The cut-off value was accepted as 640 and the patients stratified according to SII level as low and high. The progression-free survival (PFS), overall survival (OS) and overall response rate (ORR) differences between SII low and high groups have investigated The correlation between SII and PFS was also evaluated.

Results: Totally, 50 patients enrolled to study. Twenty-eight of 50 were stratified to SII high group and 22 of 50 to SII low group. Median follow-up time from diagnosis was 25 months. Median PFS was significantly longer in SII low group than SII high group (24.01 vs. 7.8 months; p=0.024). Overall survival was also significantly longer in SII low group compare with SII high group (NR vs. 29.08 months; p=0.001). the significantly negative correlation between PFS and SII was also detected (r=-0.355; p=0.011).

Conclusion: SII, a non-invasive, easily accessible - assessable marker, can be used as a prognostic marker in NSCLC with ALK-rearrangement, according to results of our study.

Keywords: ALK-rearrangement; inflammation; peripheral blood parameter; prognostic marker

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Anaplastic lymphoma kinase (ALK) and Echinoderm microtubule-associated protein-like 4(EML-4) fusion (EML4-ALK) is recognized in 3-7% of non-small lung cancer (NSCLC). In addition to NSCLC, EML4-ALK fusion can be occurred in neuroblastoma, diffuse large B cell lymphoma, inflammatory myofibroblastic tumor, and renal cell carcinoma. In consequence of ALK rearrangement, many intracellular signal pathway including mitogen-activated protein kinase (MAPK), Janus kinase with signal transducer and activator of transcription (JAK-STAT) and phosphoinositide-3-kinase with Akt murine thymoma viral oncogene homolog (PI3K-AKT) are activated and increased proliferation and survival of cancer cells, ultimately.[1, 2] In last years, many impressive developments occurred for treatment of this rare subgroup of

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NSCLC. The favorable outcomes with tyrosine kinase inhibitors (TKI) were detected in many clinical trials which included patients with the presence of ALK rearrangement. Crizotinib, an oral ALK- TKI, is the first TKI that has been shown efficacy on ALK rearrangement positive NSCLC patients. In phase 3 PROFILE 1007 and 1010 trials, crizotinib was found significantly superior to chemotherapy in treatment naïve or previously treated patients with ALK rearrangement.[3, 4] In addition to crizotinib; alectinib, brigatinib, ceritinib, and lorlatinib are the others ALK-TKI that had efficacy in this population.[5–9]

It is known that inflammation plays a key role in cancer development and also the resistance to treatment.[10, 11] Although the exact mechanism of poor outcomes related to systemic inflammation is not clearly understood, many factors including increased cytokine secretion and inflammation-related cachexia are accused.[11] Previous studies have shown that many biomarkers, such as neutrophil to lymphocyte ratio (NLR), and platelet to lymphocyte ratio (PLR), were reflected inflammatory condition and were associated with prognosis in several types of solid tumors. [12, 13] Systemic immune-inflammation index (SII) is a novel parameter that reflected the systemic inflammation and calculated by using neutrophil, lymphocyte, and platelets count. In previous trials, the prognostic importance of SII was shown in much solid cancer including lung cancer.[14]

In our knowledge, there are no trials that investigated the prognostic value of SII on lung cancer with driver mutation. So, in this trial, we aimed that investigated the prognostic value of SII on NSCLS with ALK rearrangement and treated with crizotinib in any line.

Methods

The patients with ALK gene rearrangement and treated with crizotinib at Ankara Chest Disease and Chest Surgery Hospital between 2014-2018 years were enrolled in our study. The patient's records were obtained in an electronic database of the hospital, retrospectively. All enrolled patients were more than 18 years old, metastatic or local advance that non-eligible for curative treatment and had measurable disease as assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Exclusion criteria were followed: (1) The patients who had active infection, (2) the patients with received drugs that can be effect blood parameters, (3) the patients who had blood product transfusion within 1 month before enrolment, (4) the patients who used crizotinib less than 1 months for any reason, (5) received any ALK-TKI before crizotinib.

Before ALK analyses, all tumor samples were routinely assessed for histo-immunochemistry examination. If the tumor sample was adequate for advance examination, fluorescence in-situ hybridization (FISH) was performed for detection of ALK rearrangement. All FISH analyses were done in experienced laboratories. Minimum 50 cells were counted for detection of break-apart, and the presence of more than 15% split or isolated red signals was accepted as ALK gene rearrangement positive.

SII was calculated by using formula as follow: (Neutrophil x Platelets)/ Lymphocyte. Complete blood count (CBC) and the other blood parameters were obtained at the diagnosis and before the initiation of any treatment. Cut off value for SII was accepted as 640 according to results of meta-analyses which included 2786 patients with lung cancer from 7 studies.[14] The patients with SII level ≥640 and <640 were accepted as high SII and low SII, respectively. The primary endpoint was progression-free survival for crizotinib and secondary end-points was overall survival and overall response rate. Progression-free survival (PFS) was described as the time from initiation of crizotinib to RECIST-defined progression or death. Overall survival (OS) was defined as the time from diagnosis to death. Tumor response was evaluated by CT scan or 18-FDG PET BT scan according to the Response Evaluate Criteria for Solids Tumors (RECIST). Complete response (CR) was defined as total regression of all assessable lesions; partial response (PR) was defined as the disappearance of at least 30% in the sum of the longest diameters of the target lesions; progressive disease (PD) was defined as more than a 20% increase in primary tumor volume or appearance of new lesions; the remaining patients who did not meet the criteria of PD or PR were categorized as stable disease (SD). The objective response rates were calculated by sum of CR and PR rate.

Statistical analyses were performed using the SPSS software version 23. Categorical variables were compared using The Chi-square or Fisher's exact test, where appropriate. The variables were investigated using visual (histogram, probability plots) and analytic methods (Kolmogorov-Smirnov/ Shapiro-Wilk's test) to determine whether or not they are normally distributed. Mann-Whitney-U test was used to compare non-normal disturbed and ordinal variables with the groups with high and low SII. While investigating the association between non-normally distributed and/or ordinal variables, the correlation coefficients and their significance were calculated using the Spearmen test. The effect of SII on survival outcomes was investigated using the log-rank test. The Kaplan-Meier survival estimates were calculated. Cox regression analyses were performed due to determine hazard assumption. The proportional hazard assumption and model fit was assessed by means of residual analysis. A 5% Type-I error level was used to infer statistical significance. A p-value of less than 0.05 was considered to show a statistically significant result.

Local Clinical Research Ethics Committee's approval was obtained.

Results

Totally, 50 patients who diagnosed advances NSCLC with ALK rearrangement and received crizotinib at any treatment line were enrolled to study. All patients had adenocarcinoma histology. Median age was 51,5 years (min-max; 26-76). Percentage of male and female patients were 56% and 44%, respectively. Most of the patients were non-smoker (68.3%) and 26.8% of patients were ex-smoker. Only a small subset of the patients were active smoker when initiation of treatment with crizotinib (4.9%). At the time of starting crizotinib, 85.2% of patients were metastatic and 14.6% of patients were also local advance and not suitable for local curative treatment (radiotherapy and surgery). The most commons metastatic site were contralateral lung (44%), brain (35.8%), pleura (35%), bone (28%), adrenal gland (20%) and liver (14.3%), respectively. When the patients were stratified according to crizotinib treatment line, 48% of patients received crizotinib as first-line treatment, 38% of patients received crizotinib as second-line (After one prior platinum-based regimen) and 14% of patients also received as third-line or more.

The patients stratified according to SII level; 28 of 50 patients to high SII group (≥640) and 22 of 50 patients to low SII (<640) group. The baseline characteristics of the patients were well balanced between the two groups except for adrenal gland metastasis and C-reactive protein (CRP) level. The detailed comparison of clinic feature between low and high SII group was shown in Table 1.

Median follow-up time from diagnosis was 25 months. Among 50 patients, 37 had disease progression or died by the time of data cut off. Median PFS for crizotinib was 24.01 months (CI 95%; 18.4-29.5) in the low SII group as compared with 7.8 months CI 95%; 5.3-10.3) in the high SII groups. This difference was found as statistical significant (p=0.024) (Fig. 1). The relative risk of progression or death with crizotinib was 2.12 times more in high SII group compare with low SII (Hazard Ratio: 2.12, CI 95%: 1.08-4.15). Twelve and 24 months PFS rates were 76% and 45% for low SII groups and also 39% and 24% for high SII group, respectively. The correlation analysis was performed by using the Spearman test due to non-normally distributed and the negative correlation between SII and PFS was detected (r=-0.355; p=0.011) (Fig. 2).

At the time of data cut off, 22 deaths occurred in the total population. OS was significantly longer in low SII group compare with high SII group. Median OS was 29.07 months (CI 95% 19.2-38.8) in high SII group and not reached in low SII group, respectively (p=0.001) (Fig. 3). Thirty-six months survival rate was 78% for low SII group and 42% for high SII group. The overall response rate was nearly significant

Table 1. Basal clinic-pathologic feature of patients according to SII level

Parameter	Low SII	High SII	p
Sex (M/F)	12/10	16/12	0.85
Age (median)	50.5	52	0.83
Stage			0.95
Local advance	3	4	
Metastatic	19	24	
Crizotinib treatment line			0.10
First	8	16	
Second	12	7	
Third and more	2	5	
Brain metastasis (Y/N)	10/14	8/18	0.33
Liver metastasis (Y/N)	6/23	12/10	0.40
Adrenal metastasis (Y/N)	1/21	9/19	0.015
Contralateral lung metastasis (Y/N)	12/10	10/18	0.18
Bone metastasis (Y/N)	4/18	10/18	0.171
Pleura metastasis (Y/N)	6/16	12/16	0.25
Haemoglobin (median-mg/dl)	13.2	12.8	0.61
LDH (median-mg/dl)	234	225	0.81
Albumin (median-mg/dl)	4.2	3.8	0.071
CRP	0.58	2.25	0.030

M: Male; F: Female; Y: Yes; N: No; LDH: Lactate dehydrogenase; CRP: C-reactive protein; SII: Systemic immune-inflammation index.

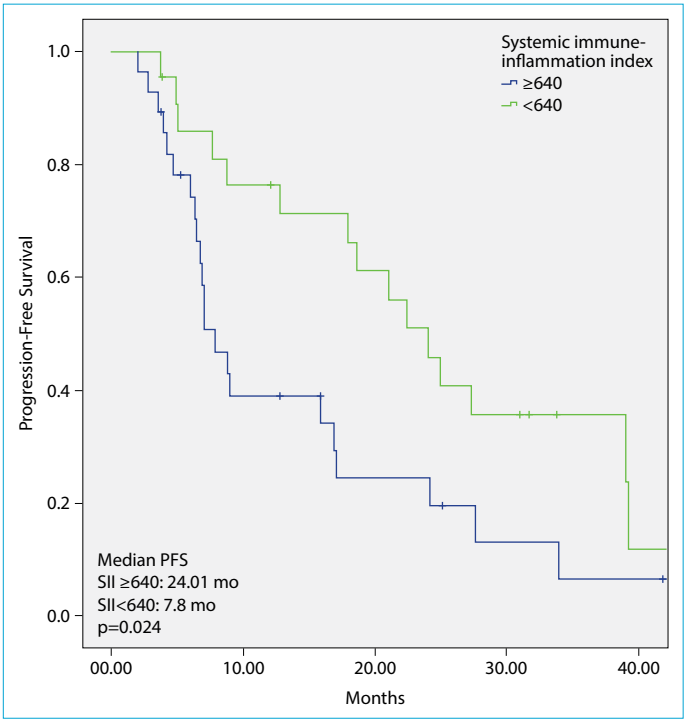

Figure 1. Progression-free survival in systemic immune-inflammation index low and high groups.

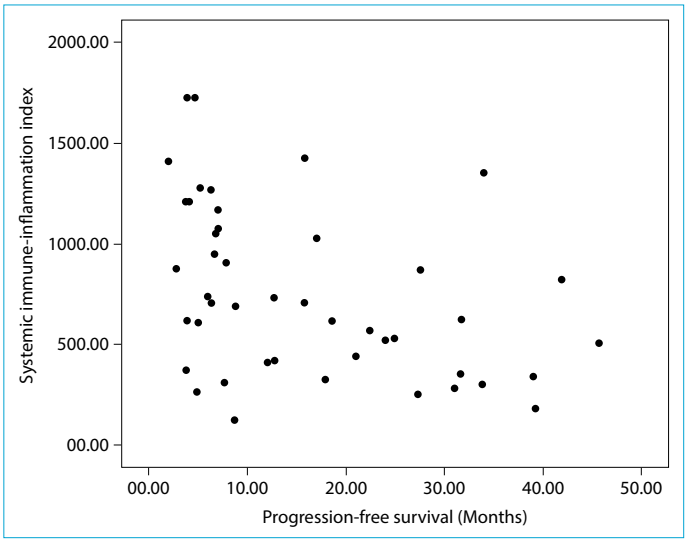

Figure 2. Correlation between systemic immune-inflammation index and progression-free survival.

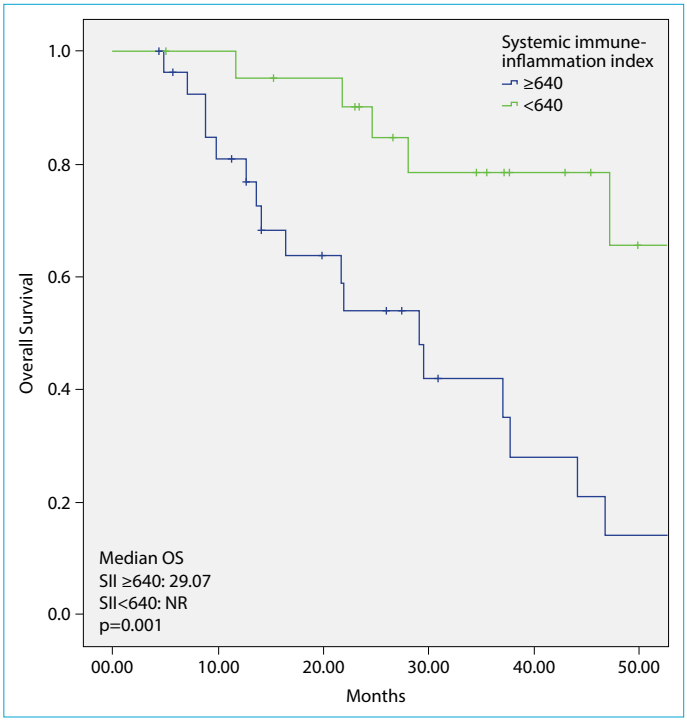

Figure 3. Overall survival in systemic immune-inflammation index low and high groups.

higher in low SII group than high SII group (86.4% vs. 64.3%; p=0.077).

Discussion

In our study, we assessed the prognostic value of SII in NSCLS with ALK rearrangement and received crizotinib at any treatment-line. We found that SII can be used as the prognostic. In the patients with low SII, mPFS and mOS were significantly longer than high SII group. Despite the difference of ORR was not statistically significant, ORR was approximately 20% more in low SII group compare with high SII. In addition, we also found a negative correlation between SII and PFS. In our knowledge, this is the first trial that investigated the prognostic importance of SII in NSCLC with ALK rearrangement and treated with crizotinib.

It is well known that there is a strong relationship between inflammation and cancer. Firstly, Virchow described the connection between inflammation and cancer in 1863.[15] Inflammation can be promoted proliferation, angiogenesis, invasion, developed metastasis and also can be inhibited apoptosis and host-immune defence systems due to several mechanism including increased secretin of cytokines, chemokines, free oxidative stress radicals, matrix metalloproteinase -9 (MMP-9), vascular endothelial growth factor (VEGF) and direct toxic effect of DNA (induced mutation etc.).[16, 17] In the light of literature, there are several trials that investigated the prognostic value of inflammation on various cancer and several markers were used to reflecting on the inflammatory condition in these trials. Neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), CRP, albumin, and sedimentation are the most commonly used marker. NLR and PLR are non-invasive, easily assessable and reproducible markers for reflection of inflammation. Increased level of NLR and PLR were found as associated with poor prognosis in many types of cancer including lung cancer.[18, 19] Neutrophils and platelets can promote tumorigenesis, invasion, and metastasis via secretion of cytokines, chemokines (MMP-9, VEGF, etc.) and increased invasion and epithelial-mesenchymal transition capacity of circulating tumor cells (CTC).[20–22] On the other hand, lymphocyte plays an important role in suppressing tumor cell proliferation and migration via secreting cytokines and ultimately, induced host-immunity. Because of that, increased NLR and PLR are associated with poor prognosis in various types of cancer.

SII is a novel marker that reflects the inflammatory condition and calculated by using neutrophil, lymphocyte, and platelet. Firstly, the prognostic value of SII was demonstrated in hepatocellular cancer.[23] Last years, many studies that investigated the prognostic importance of SII in various cancer including lung cancer were published. In these previous studies, increased SII was found associated with poor prognosis.[14, 24–26] Because of using three potential prognostic parameters together for calculation of SII, it is hypothesized that SII can be superior for reflection to inflammation rather than NLR and PLR. The results of the previous two studies which evaluated SII, NLR and PLR in esophageal and small cell lung cancer supported this hypothesis.[27, 28] In these studies, SII was found a better marker to predict

prognosis rather than NLR and PLR. Although SII was found associated with prognosis in various cancer type, there are no studies that evaluated the prognostic value of SII in lung cancer which had driver mutation and also treated with targeted therapy.

In light of the literature, there are only a few studies which detected the prognostic association between CBC parameters and EGFR-TKI therapy in EGFR-mutant NSCLC. In the first study, Zhang et al. found that NLR was an independent prognostic factor for PFS and OS in EGFR-mutant NCSLC that treated with Erlotinib or Gefitinib.[29] And the second study, the results were similar to the previous study, NLR was found as a prognostic marker for PFS and OS.[30] Both of the studies, low NLR was found associated with good outcomes. In our study, the results were correlated with previous studies. Low SII level was predicted to long PFS and OS and also significant negative correlation was found between SII and PFS. In our knowledge, this is the first study that evaluated the prognostic value of pre-treatment peripheral blood parameters in NSCLC with ALK-rearrangement. Our results are possible arose to the effect of the neutrophil, platelet, and lymphocyte in tumorigenesis and metastasis biology, as we discussed above. However, further studies are needed to clarifying the exact mechanisms of the association between peripheral blood parameters and disease outcomes.

The major limitation of our study follows: (1) retrospective design, (2) relative low number of patients, (3) enrolled only patients who received crizotinib and exclude the patients who treated with the next generation ALK-TKI in first-line. Because of having been sufficient follow-up time with crizotinib for evaluation of the prognostic value of SII in real life, we enrolled the patients who received crizotinib rather than the next generation ALK-TKI (Alectinib, Brigatinib, and Ceritinib). Thus, our findings with crizotinib may also be projected to other TKI. In our study, CRP level and rate of the adrenal gland metastasis were significantly differenced in SII low and high group. The difference of CRP between two groups is an expected finding because of CRP is another parameter that reflects inflammatory condition in the human body. On the other hand, adrenal gland metastasis does not affect the survival as much as critical organ metastasis (like as brain, liver etc.). Thus, we ignored the difference of adrenal gland metastasis ratio between SII low and high group.

In conclusion, we found that SII was negatively correlated with PFS and also low SII (<640) was predict to longer PFS and OS. Last years, many complex markers like as ALK variants or presence of co-mutation have been investigated for predict to treatment response and survival outcomes. In addition, many markers are still investigating yet. SII, a non-invasive, easily accessible - assessable and also cheap marker, can be used as a prognostic marker in NSCLC with ALK-rearrangement, according to results of our study. However, further studies are needed for validation of our results.

Disclosures

Ethics Committee Approval: Local Clinical Research Ethics Committee's approval was obtained (Ataturk Chest Disease and Chest Surgery Education and Research Hospital, 624-19.4.2019).

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Conflict of Interest: None declared.

Authorship Contributions: Concept – B.B.; Design – B.B.; Supervision – S.Y.; Materials – B.B., S.Y.; Data collection and/or processing – B.B., S.Y.; Analysis and/or interpretation – B.B.; Literature search – B.B.; Writing – B.B., S.Y.; Critical review – B.B., S.Y.

References

1. Chiarle R, Voena C, Ambrogio C, Piva R, Inghirami G. The anaplastic lymphoma kinase in the pathogenesis of cancer. Nat Rev Cancer 2008;8:11–23.
2. Ziogas DC, Tsiara A, Tsironis G, Lykka M, Liontos M, Bamias A, et al. Treating ALK-positive non-small cell lung cancer. Ann Transl Med 2018;6:141.
3. Shaw AT, Kim DW, Nakagawa K, Seto T, Crino L, Ahn MJ, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med 2013;368:2385–94.
4. Solomon BJ, Mok T, Kim DW, Wu YL, Nakagawa K, Mekhail T, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med 2014;371:2167–77.
5. Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim DW, et al. Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer. N Engl J Med 2017;377:829–38.
6. Camidge DR, Kim HR, Ahn MJ, Yang JC, Han JY, Lee JS, et al. Brigatinib versus Crizotinib in ALK-Positive Non-Small-Cell Lung Cancer. N Engl J Med 2018;379:2027–39.
7. Solomon BJ, Besse B, Bauer TM, Felip E, Soo RA, Camidge DR, et al. Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study. Lancet Oncol 2018;19:1654–67.
8. Novello S, Mazieres J, Oh IJ, de Castro J, Migliorino MR, Helland A, et al. Alectinib versus chemotherapy in crizotinib-pretreated anaplastic lymphoma kinase (ALK)-positive non-small-cell lung cancer: results from the phase III ALUR study. Ann Oncol 2018;29:1409–16.
9. Shaw AT, Kim TM, Crino L, Gridelli C, Kiura K, Liu G, et al. Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2017;18:874–86.
10. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related in-

flammation. Nature 2008;454:436–44.
11. Diakos CI, Charles KA, McMillan DC, Clarke SJ. Cancer-related inflammation and treatment effectiveness. Lancet Oncol 2014;15:e493–503.
12. Li X, Dai D, Chen B, Tang H, Xie X, Wei W. The value of neutrophil-to-lymphocyte ratio for response and prognostic effect of neoadjuvant chemotherapy in solid tumors: A systematic review and meta-analysis. J Cancer 2018;9:861–71.
13. Akinci Ozyurek B, Sahin Ozdemirel T, Buyukyaylaci Ozden S, Erdogan Y, Kaplan B, Kaplan T. Prognostic Value of the Neutrophil to Lymphocyte Ratio (NLR) in Lung Cancer Cases. Asian Pac J Cancer Prev 2017;18:1417–21.
14. Zhang Y, Chen B, Wang L, Wang R, Yang X. Systemic immune-inflammation index is a promising noninvasive marker to predict survival of lung cancer: A meta-analysis. Medicine (Baltimore) 2019;98:e13788.
15. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet 2001;357:539–45.
16. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell 2010;140:883–99.
17. Lu H, Ouyang W, Huang C. Inflammation, a key event in cancer development. Mol Cancer Res 2006;4:221–33.
18. Zhao QT, Yang Y, Xu S, Zhang XP, Wang HE, Zhang H, et al. Prognostic role of neutrophil to lymphocyte ratio in lung cancers: a meta-analysis including 7,054 patients. Onco Targets Ther 2015;8:2731–8.
19. Wang L, Liang D, Xu X, Jin J, Li S, Tian G, et al. The prognostic value of neutrophil to lymphocyte and platelet to lymphocyte ratios for patients with lung cancer. Oncol Lett 2017;14:6449–56.
20. Labelle M, Begum S, Hynes RO. Direct signaling between platelets and cancer cells induces an epithelial-mesenchymal-like transition and promotes metastasis. Cancer Cell 2011;20:576–90.
21. Bausch D, Pausch T, Krauss T, Hopt UT, Fernandez-del-Castillo C, Warshaw AL, et al. Neutrophil granulocyte derived MMP-9 is a VEGF independent functional component of the angiogenic switch in pancreatic ductal adenocarcinoma. Angiogenesis 2011;14:235–43.
22. Kolaczkowska E, Kubes P. Neutrophil recruitment and function in health and inflammation. Nat Rev Immunol 2013;13:159–75.
23. Aino H, Sumie S, Niizeki T, Kuromatsu R, Tajiri N, Nakano M, et al. The systemic inflammatory response as a prognostic factor for advanced hepatocellular carcinoma with extrahepatic metastasis. Mol Clin Oncol 2016;5:83–8.
24. Yang R, Chang Q, Meng X, Gao N, Wang W. Prognostic value of Systemic immune-inflammation index in cancer: A meta-analysis. J Cancer 2018;9:3295–302.
25. Feng JF, Chen S, Yang X. Systemic immune-inflammation index (SII) is a useful prognostic indicator for patients with squamous cell carcinoma of the esophagus. Medicine (Baltimore) 2017;96:e5886.
26. Guo D, Zhang J, Jing W, Liu J, Zhu H, Fu L, et al. Prognostic value of systemic immune-inflammation index in patients with advanced non-small-cell lung cancer. Future Oncol 2018;14:2643–50.
27. Hong X, Cui B, Wang M, Yang Z, Wang L, 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.
28. Geng Y, Shao Y, Zhu D, Zheng X, Zhou Q, Zhou W, et al. Systemic Immune-Inflammation Index Predicts Prognosis of Patients with Esophageal Squamous Cell Carcinoma: A Propensity Score-matched Analysis. Sci Rep 2016;6:39482.
29. Zhang Y, Feng YC, Zhu HG, Xiong TC, Hou YS, Song J, et al. The peripheral blood neutrophil-to-lymphocyte ratio is a prognostic predictor for survival of EGFR-mutant nonsmall cell lung cancer patients treated with EGFR-TKIs. Medicine (Baltimore) 2018;97:e11648.
30. Ding PN, Roberts TL, Chua W, Becker TM, Descallar J, Yip PY, et al. Clinical outcomes in patients with advanced epidermal growth factor receptor-mutated non-small-cell lung cancer in South Western Sydney Local Health District. Intern Med J 2017;47:1405–11.