Clinics in Oncology

Research Article
Published: 27 May, 2024

Evaluation of Systemic Immune Inflammation (SII) Index in Oral Squamous Cell Carcinoma - Exploring its Role as a Predictor Marker for Recurrence

Kalyani N and Chandra J*

Department of Oral and Maxillofacial Surgery, Yenepoya Dental College, India

Abstract

Purpose: Oral Squamous Cell Carcinoma (OSCC) is a major cause of morbidity and mortality each year. Various biomarkers like Neutrophil-Lymphocyte Ratio (NLR), Platelet Lymphocyte Ratio (PLR), have been validated as prognostic indicators. The Systemic Immune Inflammation (SII) index which combines neutrophils, lymphocytes, and platelets, was recently developed as a collaborative tool to provide prognostic information for patients with hepatocellular carcinoma, and pancreatic cancer, and germ cell tumors. This study aims to evaluate the relevance of the SII index in OSCC, to explore its role as a predictor marker for predicting recurrences, node involvement.

Methods: 34 patients with biopsy-proven OSCC fulfilling the inclusion and exclusion criteria were enrolled in this longitudinal study. SII index were calculated at three-time intervals – preoperatively, at 6- and 12-months postoperatively.

Results: On comparing the values of the SII index over 1 year with the treatment modality chosen (with RT and without RT), higher values were noted in the patients who underwent surgery with RT. SII values in relation to different TNM stages were seen as statistically significant at 1 year with a steady increase in values in T2 and T3 groups. Recurrence was seen only in one patient who had also shown a significant rise in SII values post-surgery.

Conclusion: According to our study, we can conclude that the SII index at regular intervals could be used to identify patients with an increased chance of recurrence.

Keywords: Platelets; Neutrophils; Lymphocyte; SII; OSCC; Recurrence; Predictor; TNM; Radiotherapy; Prognosis

OPEN ACCESS

Correspondence:
Nupur Kalyani, Department of Oral and Maxillofacial Surgery, Yenepoya Dental College, Mangalore, Karnataka, India,

Received Date: *08 Apr 2024*
Accepted Date: *21 May 2024*
Published Date: *27 May 2024*

Citation:
Kalyani N, Chandra J. Evaluation of Systemic Immune Inflammation (SII) Index in Oral Squamous Cell Carcinoma - Exploring its Role as a Predictor Marker for Recurrence. Clin Oncol. 2024; 9: 2074.

ISSN: 2474-1663

Background

Oral Squamous Cell Carcinoma (OSCC) is a type of cancer that develops from the lip, tongue, gingiva, cheek, the floor of the mouth, or alveolus. SCC accounts for roughly 90% of all oral neoplasms. It ranks 8th in the world in terms of cancer incidence, with epidemiologic differences between geographic regions (3rd most common malignancy in south-central Asia) [1]. Despite substantial progress in targeted therapy over the past decades, the 5-year life expectancy for OSCC is 60%, which can vary from 10% to 82% depending on the stage, age, race, comorbidity, and location in the oral cavity [2]. Nicotine use, substance misuse, and Human Papillomavirus (HPV) infection are all widely known etiologic hazards for OSCC [3,4].

Surgery only modality has been recommended for patients with early-stage tumors, and surgery or radical concurrent chemoradiotherapy is recommended for patients with advanced-stage tumors, according to the National Cancer Network [5,6].

Despite advances in surgery and postsurgical RT, disease management and overall survival continue to be challenging [7]. The stage of the tumor has a massive impact on the outcome of OSCC [8]. At the time of diagnosis, more than half of patients with oral cancer have advanced disease [9] making screening for recurrences critical in the first 5 years after treatment [8].

The poor long-term survival and scarcity of optimized biomarkers for OSCC bring us to the dire need for the development and validation of a biomarker for enhanced patient stratification, treatment decision making, and prognostic prediction [10].

Inflammation has proven to influence tumor risk and have an impact on all stages of

tumorigenesis, spurring the initial genetic mutation or epigenetic mechanism and boosting tumor development, dissemination, and advancement. Inflammatory biomarkers are becoming a popular research topic because of their low cost and ease of use [10].

Inflammatory and immune cells such as neutrophils, platelets, and lymphocytes not only stimulate cancer overgrowth, invasion, and chemoresistance in the local tumor environment, but also aid in metastasis by aiding tumor cell extravasation, the viability in peripheral blood, and subsequent reseeding at distant sites [11]. Inflammation also affects immune surveillance and responses to therapy. Immune cells that infiltrate tumors engage in extensive and dynamic crosstalk with cancer and have been recognized as emerging hallmarks of cancer and increasingly been exploited as diagnostic and therapeutic targets with translational promise [12,13]. Quantifications of peripheral cells of the immune system such as neutrophils, platelets and lymphocytes, as well as their ratios, have been found and affirmed as novel biomarkers of prognostic value in a range of malignancies, according to these studies [10].

Various biomarkers, those of lymphocyte count, Neutrophil-Lymphocyte Ratio (NLR), Platelet Lymphocyte Ratio (PLR), and C-Reactive Protein, have been developed and validated as prognostic indicators of various cancers (CRP). The Systemic Immune Inflammation (SII) Index was recently developed as a collaborative tool to provide prognostic information for patients with hepatocellular carcinoma, pancreatic cancer, and germ cell tumors. It is based on neutrophils, lymphocytes, and platelets. This new integrated prognostic score, which combines peripheral neutrophils, lymphocytes, and platelets, outperforms individual cell-based factors in prognosis assessment, most likely because it provides more accurate mapping of host inflammation and immune status. However, the predictive value of these inflammatory and hematological markers in OSCC is still being disputed [11].

Thus, this study aims to evaluate the relevance of the SII index in OSCC, to explore its role as a predictor marker for predicting recurrences, node involvement.

Methods

The study was approved by the institutional ethics committee and was performed in accordance with the ethical standards laid down in the Declaration of Helsinki. Informed consent was obtained for all participants.

This was a longitudinal study where 34 histologically diagnosed OSCC patients who underwent surgery, or a combination of surgery and radiation therapy were assessed. The sample size was calculated based on 5% level of significance, 80% power and an effect size of 0.5.

Neutrophil (N), Lymphocyte (L) and Platelets (P) values at three different intervals (pre operatively, 6 months post-surgery and 1-year post-surgery) was evaluated with the help of SII ($P \times N/L$) index.

The inclusion criteria for the study comprised of biopsy proven, previously untreated oral squamous cell carcinoma patients. Patients having no history of another cancer, patients undergoing multi-modality treatment (surgery/surgery with radiation) with curative intent and patients having no evidence of distant metastasis.

Patients who underwent preoperative or postoperative chemoradiotherapy or those with clinical evidence of infection or inflammation that would acutely or chronically evoke a systemic inflammatory response, patients with active infection or inflammatory disease within 4 weeks before preoperative standard blood harvest and test were excluded, patients with hematological disorders or treatment that may influence laboratory parameters and patients with autoimmune disease or undergoing any treatment with steroids were excluded from the study.

Patients following curative resection were followed up every month during the first one-year postoperative period.

If any suspicious lesions were found at follow-up visits, CT or MRI scan together with biopsy were performed. The SII values were again evaluated. If local recurrence or metastasis was present, second radical resection or RT/CT was given as appropriate.

Results

The 34 patients were categorized in two groups based on the treatment modality-Group 1 (patients who underwent surgery and radiotherapy) and group 2 (patients who underwent surgery only approach). Group 1 consisted of 18 patients and group 2 comprised of 16 patients. Furthermore, based on their TNM stage the patients were also categorized into 4 groups- T1 group (5), T2 group (21), T3 group (7), T4 group (2).

Out of the 34 patients who participated in the study, there was 26 male and 8 female with a mean age of 48 years (35-71 years).

The data were analyzed using SPSS (Statistical Package for Social Science Program) version 23. Independent-*t* test and ANOVA test was used to compare the SII values in relation to treatment modality and the stage of OSCC.

As seen in Table 1, the independent *t*-test which was done between Group 1 and Group 2, showed no statistical difference in the SII values of the two groups at the different periods.

ANOVA test was done to see the SII values in relation to the different T groups. As seen in Tables 2-4 statistical significance was only seen in the SII values of 1 year among the tumor groups (highest for T3 group) whereas the values pre-operatively and at 6 months was statistically insignificant.

Furthermore, as seen in Graph 1, the plotted ROC curve

Table 1: Intergroup comparison between SII values and the treatment group.

		N	Mean	Standard Deviation	p-value
SII Pre	With RT	18	834.27	748.42	0.744
	Without RT	16	742.72	872.77	
SII 6 Month	With RT	18	1381.29	1049.86	0.066
	Without RT	16	807.62	627.21	
SII 1 Year	With RT	18	1381.07	918.97	0.174
	Without RT	16	1013.69	552.65	

p-value based on Independent-*t*-Test
* = Statistically Significant (p<0.05)

Table 2: Comparison between pre operative SII with tumor groups.

		N	Mean	Standard Deviation	p-value
SII Pre	T1	5	445.12	155.86	0.604
	T2	21	803.81	786.13	
	T3	7	1005.72	1125.63	
	T4	2	401.18	38.57	

p-value based on ANOVA (Analysis of Variance) Test
* = Statistically Significant (p<0.05)

Table 3: Comparison between 6-month SII with tumor groups.

		N	Mean	Standard Deviation	p-value
SII 6 Month	T1	5	486.44	227.76	0.168
	T2	21	1053.07	754.24	
	T3	7	1656.41	1392.62	
	T4	2	1177.52	601.02	

p-value based on ANOVA (Analysis of Variance) Test
* = Statistically Significant (p<0.05)

Table 4: Overall intra-group comparison- SII 1 year.

		N	Mean	Standard Deviation	p-value
SII 1 Year	T1	5	639.15	330.95	0.043*
	T2	21	1101	690.06	
	T3	7	1828.59	1004.33	
	T4	2	1506.68	49.61	

p-value based on ANOVA (Analysis of Variance) Test
* = Statistically Significant (p<0.05)

Table 5: ROC Analysis (T groups).

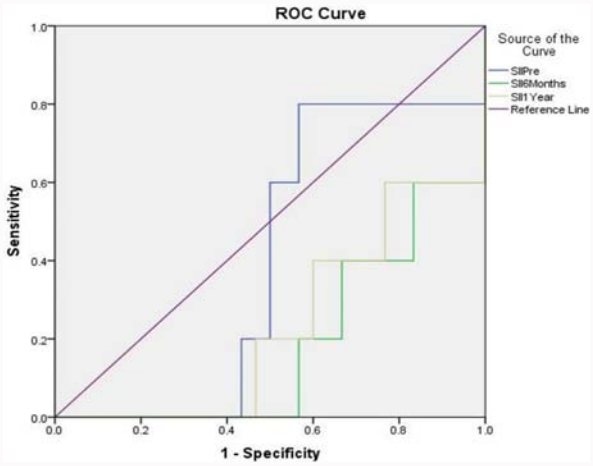
ROC Analysis – Area under the Curve (Plotted against Standard and Test Variables)		
Test Variables	**Area**	**p-value**
SII Pre	0.4	<0.001*
SII 6 Months	0.187	<0.001*
SII 1 Year	0.233	<0.001*

* = Statistically Significant (p<0.05)

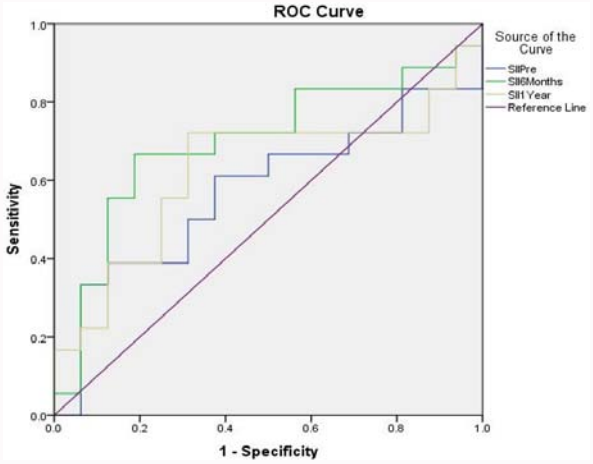
Table 6: ROC analysis (Treatment modality).

ROC Analysis – Area under the Curve (Plotted against Standard and Test Variables)		
Test Variables	**Area**	**p-value**
SII Pre	0.573	<0.001*
SII 6 Months	0.698	<0.001*
SII 1 Year	0.625	<0.001*

* = Statistically Significant (p<0.05)



Graph 1: Receiver Operator Curve (ROC) graph analysis (T groups).



Graph 2: Receiver Operative Curve (ROC) graph analysis (Treatment modality).

showed that SII preoperatively and at 1 year was better identified in comparison to SII at 6 months while all three test variables were statistically significant.

Similarly, Graph 2 showed the ROC curve plotted with treatment modality chosen (Surgery alone and Surgery with Radiotherapy) as the standard variable and SII index preoperatively 6 months and 1 year as the test variables. The plotted curve showed that SII at 6 months and 1 year was better identified in comparison to SII preoperatively while all three test variables were statistically significant.

Discussion

The dismal long-term survival and paucity of optimized biomarkers for OSCC highlight the pressing need to identify effective prognostic biomarkers and regimes to better patient stratification and treatment planning [14]. In our study, we determined the SII values at spaced intervals and their relation to, histopathological staging, treatment modality and recurrence. Our finding further supports the prognostic significance of these biomarkers in OSCC.

The SII index, which is based on neutrophils, lymphocytes, and platelets, has recently been developed as a joined tool to provide prognostic information in patients with hepatocellular carcinoma, pancreatic cancer, and germ-cell tumor [15-17]. This novel integrated prognostic score are more powerful in prognostic assessment than individual cell type-based factors, presumably because it better reflects the balance of host inflammation and immune status [18,19].

Platelets secrete cytokines and growth factors such as transforming growth factor-β, Vascular Endothelial Growth Factor (VEGF), matrix metalloproteinase-2, platelet factor-4, and platelet-derived growth factor which in turn induce hallmarks of cancer progression such as epithelial-mesenchymal transition, angiogenesis, cell migration, and/or proliferation and also facilitate the retention of tumor emboli in microcirculation [20]. Platelets also stimulate the release of pro-inflammatory cytokines (interleukin 1, 3, and 6) by cancer cells which are involved in tumor angiogenesis and further tumor inflammation [20]. Thus, platelets are essential and have a multifunctional role in cancer development [21].

Neutrophils are key mediators of the innate immune system. Neutrophil activation is essential to protect the host system against infections and promote normal healing [22,23]. For many decades, leukocytosis has been associated with poor prognosis in different types of malignancies [24-27].

It is thought that the initial immune response to an early neoplasm mirrors the response to acute tissue injury, with sequential infiltration by various myeloid populations leading to eventual

infiltration by lymphocytes [28]. Li et al. found differences in survival associated with platelet or platelet-lymphocyte ratio counts, revealing that higher counts were associated with worse survival, with platelet count being a surrogate marker of inflammation and lymphocyte count with immune status [29].

A mean cut-off value of 779.98 was derived from all pre-operative SII values of all 34 patients. On categorizing the patients under high SII (>779.98) and low SII (<779.98), it was seen that 9/34 patients had a preoperative high SII which remained considerably high at 6 months and 1 year in 6/9 patients whereas for other 3 a decrease in the SII value was observed at 6 months and 1 year. This could be attributed to the histopathological grading and the treatment modality for the 3 patients as the 6 patients belonged to T3 group. One out of those patients showed recurrence in the 9th month. Zhiyuan Lu et al. in their study also found a high preoperative SII (>569) significantly related to tumor size, histological grade, depth of invasion, Lymph Node Density (LND) [30].

In our study, patients with high SII values were mostly the patients belonging to either T2/T3 group and undergoing curative resection along with adjuvant RT. In the intergroup comparison (Table 3) done between the patients undergoing surgical resection with adjuvant RT (n=18) and only surgical resection (n=16), we noted a higher mean of SII (779.98) at all three-time intervals (preoperatively, 6 months and 1 year) in patients with combined treatment modality (*i.e.*, surgery and RT). 25 out of 34 patients could be put in preoperative SII <779.989. Out of these 25 patients, 9 patients belonged to T2 or T3 group, who underwent surgical management with adjuvant therapy and showed a considerable increase in SII values at 6 months (Table 3) and 1 year (Table 4). Even though the 6 months and 1-year SII in the surgery and RT group were considerably high, it was not statistically significant. But 5/16 patients who underwent only curative resection with neck dissection in our study showed high follow-up SII value. A possibility for these high values could be associated with the risk factors like habit history, age of the patient, site of the lesion, etc. which needs further evaluation and follow up.

Further in our study as seen in Table 2, the mean preoperative SII values were seen considerably higher (more than the mean cut-off of 779.98) in patients belonging to T2 (803.81) and T3 (1005.72) group. This was in accordance with the study done by Mashhadiabbas et al. to establish the role of the inflammatory infiltrate and analyzed 125 samples from patients diagnosed with dysplasia (mild, moderate, or severe) or OSCC, and found a positive correlation between the intensity of inflammatory infiltrate and lesion severity, the most abundant inflammatory infiltrate was observed among OSCC patients [31]. However, in our study, we did find a lower mean (401.18) preoperative value of preoperative SII of patients with T4 group which did not correlate to the study done by Mashadiabbas et al. This lower mean value could be attributed to the fact that only 2 patients were evaluated in T4 group.

In subsequent follow-ups at 6 months (Table 3) and 1 year (Table 4), we noted consistently higher mean SII values at both time intervals in T2, T3, and T4 groups. Though the SII values in all the T stage was statistically insignificant at 6-month follow-up, it was statistically significant at 1-year follow-up with the highest mean for the T3 group. The higher mean value in the T3 group could further be correlated to the treatment modality given (curative resection with RT) in all 7 patients. Our findings of the SII index with the treatment modality and the TNM staging could be correlated to study carried by Yang et al in 2018, which was a meta-analysis to determine the prognostic value of systemic immune inflammation index in cancer and concluded by saying that high SII may be a potential prognostic marker in patients with various cancers and associated with poor overall outcomes [32].

In our study we found recurrence in only one patient who was treated for right buccal mucosa cancer without RT. The patient had a preoperative high SII value (>779.98), which remained considerably high even after the treatment and at six-month follow-up. In the 9th month, the patient had returned with recurrence with a significantly higher SII value.

Our study had a smaller sample size and a shorter follow-up as opposed to studies done in the past. Hence the ROC curve analysis (Graph 1 with Table 5 and Graph 2 with Table 6) was carried out to check for the sensitivity and specificity of the TNM staging and the treatment modality with the SII index and statistically significant results were obtained.

Cut-off value for this prognostic predictor for patient stratification varies among diverse studies and their optimal cut-off for cancer type might be a prerequisite before they are translated into clinical practice. Hence SII index could be used as an affordable biomarker in OSCC patients wherein if a standard cut off range of preoperative SII index is gained, patients could be categorized into high and low of the preoperative value. The patients with preoperative high SII should be closely monitored for recurrence. Depending on the SII value, the treatment plan can be modified to incorporate neoadjuvant/adjuvant therapy to give better results to the patients.

Conclusion

This study was conducted to evaluate the role of the Systemic Immune Inflammation (SII) index in oral squamous cell carcinoma patients and to explore the role of this index as a predictor marker for recurrence. After analyzing the results, we can conclude that SII index at regular intervals could be used to identify patients with an increased chance of recurrence. For patients showing a higher preoperative SII index and advanced stage, the treatment can also be better planned (adjuvant therapies for patient showing higher values of SII) and a more vigilant long term follow up.

References

1. Massano J, Regateiro FS, Januário G, Ferreira A. Oral squamous cell carcinoma: Review of prognostic and predictive factors. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2006;102(1):67-76.
2. National Cancer Institute. Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute Surveillance Research Program, based on November 2006 submission of SEER series 9 (1996-2003) 2006.
3. Hashibe M, Brennan P, Chuang SC, Boccia S, Castellsague X, Chen C, et al. Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. Cancer Epidemiol Biomarkers Prev. 2009;18(2):541-50.
4. Chaturvedi AK, Anderson WF, Lortet-Tieulent J, Curado MP, Ferlay J, Franceschi S, et al. Worldwide trends in incidence rates for oral cavity and oropharyngeal cancers. J Clin Oncol. 2013;31(36):4550-9.
5. National Comprehensive Cancer Network. NCCN Practice Guidelines in Oncology: Head and Neck Cancers, 2013.
6. Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefèbvre JL, Greiner

RH, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med. 2004;350(19):1945-52.

7. Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med. 2004;350(19):1937-44.
8. Vázquez-Mahía I, Seoane J, Varela-Centelles P, Tomás I, García AÁ, Cedrún JL. Predictors for tumor recurrence after primary definitive surgery for oral cancer. J Oral Maxillofac Surg. 2012;70(7):1724-32.
9. Dovšak T, Ihan A, Didanovič V, Kansky A, Verdenik M, Hren NI. Effect of surgery and radiotherapy on complete blood count, lymphocyte subsets, and inflammatory response in patients with advanced oral cancer. BMC Cancer. 2018;18(1):235.
10. Diao P, Wu Y, Ge H, Li J, Zhang W, Huang R, et al. Preoperative circulating platelet, neutrophil, and lymphocyte counts predict survival in oral cancer. Oral Dis. 2019;25(4):1057-66.
11. Diao P, Wu Y, Li J, Zhang W, Huang R, Zhou C, et al. Preoperative systemic immune-inflammation index predicts prognosis of patients with oral squamous cell carcinoma after curative resection. J Transl Med. 2018;16(1):365.
12. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell. 2010;140(6):883-99.
13. Okuyemi OT, Piccirillo JF, Spitznagel E. TNM staging compared with a new clinicopathological model in predicting oral tongue squamous cell carcinoma survival. Head Neck. 2014;36(10):1481-9.
14. Chinn SB, Myers JN. Oral cavity carcinoma: Current management, controversies, and future directions. J Clin Oncol. 2015;33(29):3269-76.
15. Shalapour S, Karin M. Immunity, inflammation, and cancer: An eternal fight between good and evil. J Clin Invest. 2015;125(9):3347-55.
16. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell. 2010;140(6):883-99.
17. Diakos CI, Charles KA, McMillan DC, Clarke SJ. Cancer-related inflammation and treatment effectiveness. Lancet Oncol. 2014;15:e493-503.
18. Weiss MH, Harrison LB, Isaacs RS. Use of decision analysis in planning a management strategy for the stage NO neck. Arch Otolaryngol Head Neck Surg. 1994;120(7):699-702.
19. Byers RM, Weber RS, Andrews T, McGill D, Kare R, Wolf P. Frequency and therapeutic implications of "skip metastases" in the neck from squamous carcinoma of the oral tongue. Head Neck. 1997;19(1):14-9.
20. Pilatova K, Greplova K, Demlova R, Bencsikova B, Klement GL, Zdrazilova-Dubska L. Role of platelet chemokines, PF-4 and CTAP-III, in cancer biology. J Hematol Oncol. 2013;6:42.
21. Buergy D, Wenz F, Groden C, Brockmann MA. Tumor–platelet interaction in solid tumors. Int J Cancer. 2012;130(12):2747-60.
22. Magalhaes MA. Effective neutrophil activation during innate immunity: Understanding the specific roles of Rac1 and Rac2 (Doctoral dissertation). 2009.
23. Mayadas TN, Cullere X, Lowell CA. The multifaceted functions of neutrophils. Annu Rev Pathol. 2014;9:181-218.
24. Shoenfeld Y, Tal A, Berliner S, Pinkhas J. Leukocytosis in non-hematological malignancies- A possible tumor-associated marker. J Cancer Res Clin Oncol. 1986;111(1):54-8.
25. Gao Q, Zhao YJ, Wang XY, Qiu SJ, Shi YH, Sun J, et al. CXCR6 upregulation contributes to a proinflammatory tumor microenvironment that drives metastasis and poor patient outcomes in hepatocellular carcinoma. Cancer Res. 2012;72(14):3546-56.
26. Carus A, Ladekarl M, Hager H, Nedergaard BS, Donskov F. Tumour-associated CD66b+ neutrophil count is an independent prognostic factor for recurrence in localised cervical cancer. Br J Cancer. 2013;108(10):2116-22.
27. Jensen TO, Schmidt H, Møller HJ, Donskov F, Høyer M, Sjoegren P, et al. Intratumoral neutrophils and plasmacytoid dendritic cells indicate poor prognosis and are associated with pSTAT3 expression in AJCC stage I/II melanoma. Cancer. 2012;118(9):2476-85.
28. Fridlender ZG, Albelda SM. Tumor-associated neutrophils: Friend or Foe? Carcinogenesis. 2012;33(5):949-55.
29. Li Z, Xu Z, Huang Y, Zhao R, Cui Y, Zhou Y, et al. Prognostic values of the preoperative platelet-to-lymphocyte ratio, albumin and hemoglobin in patients with non-metastatic colon cancer. Cancer Manag Res. 2019;11:3265-74.
30. Lu Z, Yan W, Liang J, Yu M, Liu J, Hao J, et al. Nomogram based on systemic immune-inflammation index to predict survival of tongue cancer patients who underwent cervical dissection. Front Oncol. 2020;10:341.
31. Mashhadiabbas F, Fayazi-Boroujeni M. Correlation of vascularization and inflammation with the severity of oral leukoplakia. Iran J Pathol. 2017;12(3):225-30.
32. 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(18):3295-302.