International Journal of Research and Review
Vol.7; Issue: 2; February 2020
Website: www.ijrrjournal.com
Original Research Article *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

Blood Parameters as Surrogate Markers to Predict Treatment Response after Radiation Therapy in Head and Neck Malignancies

Aathira T S[1], Sweety Gupta[2], Ajay S Krishnan[3], Debanjan Sikdar[1], Sagar Raut[1], Nidhi Sharma[1], Naseef P K[1], Deepa Joseph[4], Rajesh Pasricha[5], Manoj Gupta[6], Bela Goyal[2]

[1]Junior Resident, [2]Assistant Professor, [3]Senior Resident, [4]Associate Professor, [5]Additional Professor, [6]Professor and Head,
Dept. of Radiation Oncology, All India Institute of Medical Sciences, Rishikesh, India.

Corresponding Author: Aathira T S

ABSTRACT

Background: Several prognostic factors have been defined for Head and neck cancers that can influence response to therapy and eventual outcomes. Recent studies show that Neutrophil to Lymphocyte ratio (NLR) Platelet to Lymphocyte ratio (PLR) and Red blood cell distribution width (RDW)are hematologic makers that have started to show prognostic significance across many types of cancers.
Aim: Evaluate role of NLR, PLR and RDW as surrogate markers to predict treatment response in head and neck malignancies
Methodology: We retrospectively analysed stage II to IVB HNC treated with radical intent from Jan 2018 to Dec 2018 in the department of Radiation oncology. Inclusion criteria were new histologically confirmed head and neck squamous cell cancer.
Result: Out of 51patients analysed, 31 patients had complete response and 19 had residual/recurrence. Baseline RDW NLR and PLR ranged from10.2-20.1, 1.02-18.6 and 22.7-608.9 respectively. In complete response patients mean NLR was 2.0 (CI-1.78-2.21) which was significantly lower than mean NLR in disease which was 5.18 (CI-3.46-6.90). Mean PLR in complete response patients was 93.99 (CI-79.11-108.87) that was significantly lower than mean PLR in disease which was 218.47 (CI-158.59-278.35). There was a significantly higher RDW in disease patients with mean 16.0 (CI-15.13-16.87) than mean RDW in complete response patients which was 13.52 (CI-12.93-14.88).
Conclusion: NLR and PLR represent immunity status and also an indicator of prognosis of cancer patients. RDW is a marker of systemic inflammatory response. In our study elevated pre-treatment NLR, PLR and RDW predicted poor response to treatment.

Key words **-** Neutrophil to Lymphocyte ratio (NLR), Platelet to Lymphocyte ratio (PLR), Red blood cell distribution width (RDW), Head and Neck radiotherapy

INTRODUCTION

Head and neck cancers (HNC) are the most common malignancies in India with an incidence of 11.42% and mortality of 10.09%. [1] Currently radiation therapy is the backbone in the treatment of head and neck carcinomas. Several prognostic factors have been proven to predict prognosis and response in these patients treated with radiation like tumour stage, nodal status, distant metastases, pathology, degree of differentiation. [2] It has been evident that patients with same TNM staging are having a heterogeneous response to treatment even after completion of scheduled radiation therapy dose. This difference deviated from cancer related characteristics to various patient related factors including biomarkers of inflammation.
Hallmark of cancer is inflammation [3] and recently various biomarkers, especially haematological markers of inflammation are

being focussed which play important role in tumour progression. Systemic inflammatory response produced in human body against cancer cells and markers released plays a vital role in treatment response. Most promising results are that of neutrophil-lymphocyte-ratio (NLR), Platelet-Lymphocyte-ratio (PLR) and red cell distribution width (RDW) as a diagnostic, predictive as well as prognostic factor in gastrointestinal, breast and lung cancer. [4-8] Tumour microenvironment changes plays an important role in behaviour of tumour including complete response, progression or treatment resistance. NLR, PLR and RDW are three simple blood parameters easily available with low cost. Since role of these in head and neck carcinomas are not clearly defined, we planned a retrospective analysis to elucidate their role in treatment response.

MATERIALS AND METHODS

In this retrospective study, we examined case records of head and neck squamous cell carcinoma patients, stage II to IVB treated with radical intent from Jan 2018 to Dec 2018 in the department of Radiation oncology, AIIMS Rishikesh with concurrent chemo radiotherapy with intensity modulated radiotherapy technique (IMRT).

We included only those patients with complete records of pre-treatment blood parameters and with a minimum follow up of 6 months' post radiation therapy. Exclusion criteria were previous history of head and neck cancer, patient having inflammatory disease such as inflammatory bowel disease, rheumatic disease, and chronic infection or acute infection within 1 month of blood sample collection, patient receiving systemic corticosteroids, post Kidney transplantation, Severe anaemia, patients on iron supplementation therapy or with recent deep venous thrombosis (past 6 months) or who has received recent blood transfusion (past 3 months).

Measurement of variables

Pre-treatment Blood parameters collected from complete blood count (CBC) included white blood cells (WBCs), platelets (PLTs), and Red cell distribution width (RDW-percentage). Peripheral blood smear reports were also collected. Normal range of RDW obtained from the CBC in our institute laboratory was 11.5–14.5. NLR was calculated by dividing neutrophil count with the lymphocyte count and PLR was calculated by dividing platelet count with lymphocyte count.NLR values >2.5 [9] and PLR values >135 [10] were considered elevated based on previous studies conducted.

Statistical analysis

The data thus obtained was assessed, analyzed using the IBM SPSS 23.0 software. Continuous variable was reported as Mean±SD. p value <0.05 was considered to indicate a statistically significant result.

RESULTS

A total of 90 patient records were evaluated and 51 files with complete records were included in the study, 50 (98.03%) males and 1 (1.96%) female. Median age was 56 (30-78) years. Majority of the patients were of oropharynx (66%) followed by larynx (22%), oral cavity (8%) and hypopharynx (4%) (Table 1).

Table 1 – Patient characteristics

Patient Characteristics	N(%)
Age, years	
<60	38
>60	13
Mean	54
Gender	
Male	98.03
Female	1.96
Smoking	
Smokers	88
Non – smokers	12
Alcoholism	
Alcoholics	55
Non – alcoholics	45
Site	
Oral cavity	8
Oropharynx	66
Hypopharynx	4
Larynx	22
Stage	
I/II	8
III	23
IVA	59
IVB	10
Histology	
Well Differentiated	32
Moderately Differentiated	54
Poorly Differentiated	14

All the patients were treated with radical chemo radiotherapy by intensity modulated radiotherapy technique (IMRT). Of 51 patients, after a median follow up of 7 (2-13) months, 31 patients (60.78%) had complete response (Responders), 11 (21.56%) patients had residual disease, 5 (9.8%) had recurrence and 4 (7.84%) had metastatic disease (Non-responders).

All the variables were analysed individually and were found to be normally distributed and hence unpaired T test was used.

Table 2 – NLR, PLR and RDW parameters in responders and non-responders

Parameters	NLR (Responders)	NLR (Non-Responders)	PLR (Responders)	PLR (Non-Responders)	RDW (Responders)	RDW (Non-Responders)
Median	2.04	4.27	77.94	172.3	13.40	16.30
25th Percentile	1.45	3.23	66.43	140.6	12.50	14.50
75th Percentile	2.35	5.71	122.8	260.0	14.10	17.10
AUC	0.934		0.888		0.812	

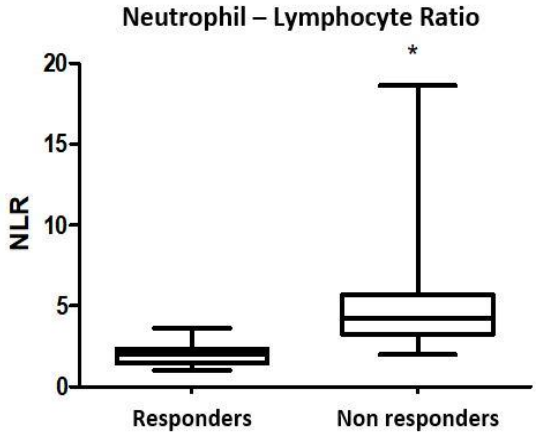

Figure 1 - Box plot showing comparison of NLR in responders and non-responders

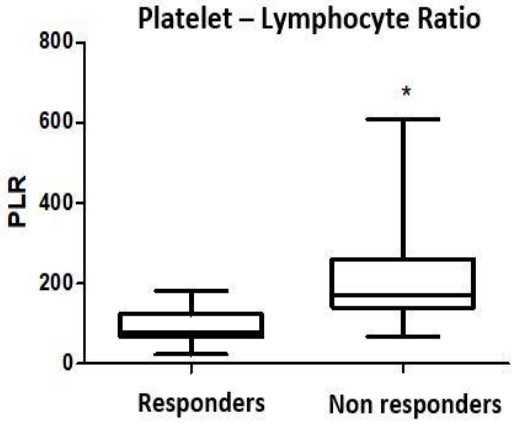

Figure 2 - Box plot showing comparison of PLR in responders and non-responders

The pre-treatment NLR ranged from 1.02-18.6. In responders mean NLR in 2.0 (CI-1.78-2.21) and in non-responders 5.18 (CI-3.46-6.90), which was significantly higher by unpaired T test (p- <0.0001). (Fig 1)

The pre-treatment PLR ranged from 22.7-608.9. The mean PLR in responders was 93.99 (CI-79.11-108.87) which was significantly lower by unpaired T test ($p < 0.0001$) in non-responders with mean 218.5 (CI-158.59-278.35). (Fig 2)

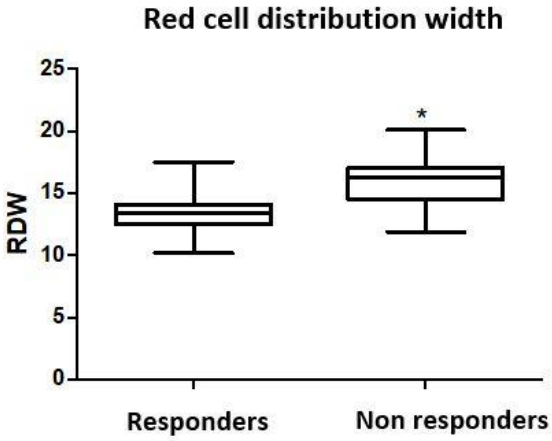

Figure 3 - Box plot showing comparison of RDW in responders and non-responders

The pre-treatment RDW ranged from 10.2-20.1 There was a significantly higher by unpaired T test (p -0.0002) RDW in non-responders with mean 16.0 (CI-15.13-16.87) than mean RDW in complete response patients which was 13.52 (CI-12.93-14.88). (Fig 3)

The ROC (**Receiver Operating Characteristics)** curve was created by plotting the true positive rate (sensitivity) against the false positive rate (1-specificity) at various threshold settings.(Fig:4) The study shows a very good discriminatory power with area under curve (AUC) >0.8

for identifying responders from non-responders.(table:2)

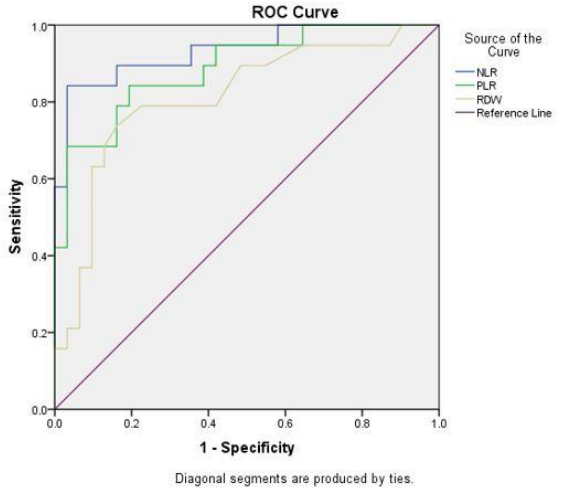

Figure 4 - ROC curve showing sensitivity and specificity of NLR, PLR and RDW

DISCUSSION

Blood parameters of systemic inflammation including NLR, PLR and RDW are currently being studied widely in various diseases including malignancies and their prognostic value has been established. In our study we evaluated 51 patients with head and neck malignancy and squamous cell histology. Patients with residual disease, recurrence or who developed distant metastasis post completion of chemo radiotherapy where found to have elevated NLR (<0.0001), PLR (<0.0001) and RDW (0.0002) when compared to patients who had complete response.

Few studies in head and neck sites has shown the role of NLR and PLR in predicting survival or treatment response with selection of one head and neck site. Also, literature reveals that studies showing role of RDW in malignancy are limited. Hence in this study we have evaluated all the three parameters for predicting treatment response and included most of the head and neck squamous cell carcinoma sites as biology of all these have been found to be same.

NLR was used in laryngeal carcinoma by Kum et al [11] and suggested that this inflammatory parameter could differentiate between benign and malignant lesions. Kara et al [12] in 2017 has conducted a study to identify the potential prognostic roles of the preoperative NLR, PLR and RDW in patients with laryngeal squamous cell carcinoma and showed similar results. Pre-treatment PLR and RDW predicted poor prognosis in laryngeal carcinoma and NLR was used a local recurrence indicator.

Another study by Tangthongkum [13] showed that high PLR was associated with poor survival and recurrence in patients with carcinoma oral cavity but RDW had no prognostic significance on any outcome. Malik et al [14] showed that poor clinicopathological factors and survival can be predicted by PLR in oral cavity cancer patients but in only those patients who received chemotherapy NLR could predicted survival.

The mechanism by which inflammatory parameters result in cancer prognosis has not been clearly understood. Various theories have been proposed to explain the individualized response against cancer cells. Neutrophil has the capability of modulating the tumour microenvironment and by release of matrix metalloprotease 9 (MMP9) and vascular endothelial growth factor (VEGF) which have a strong proangiogenic effect that results in tumour progression. [15]

Several substances are released by neutrophils that are directed against extracellular matrix (ECM) and causes ECM remodeling and release of cytokines and there is increased turnover of immature neutrophils. It has been noted that in patients with elevated NLR values there is more pro inflammatory cytokine release as shown by Motomura et al [16] and Kantola et al [17] there is release of IL - 17 IL-1ra, IL-6, IL-7, IL-8, IL-12, MCP-1, PDGFBB and increased tumour macrophage infiltration.

Role of platelet lymphocyte ratio in carcinoma is ill defined. Platelets promote tumour angiogenesis and cause capillary permeability by secretion of bio proteins that may result in tumour progression [18] and by interaction with receptors in body and promoting tumour invasion. [19]

Lymphocytes play a major role in antitumor immunity and depletion of tumour results in poor prognosis and high platelet counts is associated with lymphopenia in cancer patients. [20]

High RDW has been associated with poor survival and prognosis in many disease including cardiovascular disease, diabetes, vascular thromboembolism and cancers as a result of anisocytosis caused by inflammation, nutritional insufficiency and reactive oxygen species. [21] Dietary insufficiency in cancer patients due to iron, folic acid and vitamin B12 deficiency cause anisocytosis and immature red blood cells. Increased RDW is shown to be associated with elevated levels of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and interleukin (IL)-6 levels which cause erythroid progenitor inhibition and increased expression of hepcidin which further results in anaemia. [22] Oxidative stress further exacerbates the variation in red cell size

CONCLUSION

NLR and PLR represent immunity status and also an indicator of prognosis of cancer patients. RDW is a marker of systemic inflammatory response. In our study elevated pre-treatment NLR, PLR and RDW predicted poor response to treatment. Therefore, Blood parameters may be potential surrogate markers to predict response in adjunct to other modalities. Further studies with larger sample size are required for the same.

REFERENCES

1. Bray F, Ferlay J, Soejomataram I et al. Global cancer statistics 2018; GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancr J Clin2018; 68:394-424
2. Van den Brekel MWM, Bindels EMJ, Balm AJM. Prognostic factors in head and neck cancer. Eur J Cancer 2002; 38:1041–3.
3. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011; 144(5):646–74.
4. Kwon H.C., Kim S.H., Oh S.Y., Lee S., Lee J.H., Choi H.J., et al. Clinical significance of preoperative neutrophil-lymphocyte versus platelet-lymphocyte ratio in patients with operable colorectal cancer. Biomarkers. 2012; 17:216–222
5. Lee S., Oh S.Y., Kim S.H., Lee J.H., Kim M.C., Kim K.H., Kim H.J. Prognostic significance of neutrophil lymphocyte ratio and platelet lymphocyte ratio in advanced gastric cancer patients treated with folfox chemotherapy. BMC Cancer. 2013; 13:350.
6. Bhatti I., Peacock O., Lloyd G., Larvin M., Hall R.I. Preoperative hematologic markers as independent predictors of prognosis in resected pancreatic ductal adenocarcinoma: Neutrophil-lymphocyte versus platelet-lymphocyte ratio. Am. J. Surg. 2010; 200:197–203.
7. Ethier JL, Desautels D, Templeton A, Shah PS, Amir E. Prognostic role of neutrophil-to-lymphocyte ratio in breast cancer: a systematic review and meta-analysis. Breast Cancer Res. 2017; 19:2.
8. Yuan C, Li N, Mao X, Liu Z, Ou W, Wang SY. Elevated pretreatment neutrophil/white blood cell ratio and monocyte/lymphocyte ratio predict poor survival in patients with curatively resected non-small cell lung cancer: results from a large cohort. Thorac Cancer. 2017; 8:350-358.
9. Forget P, et al. What is the normal value of the neutrophil-to-lymphocyte ratio. BMC Res Notes. 2017; 10:12
10. Chen S, Guo J, Feng C, Ke Z, Chen L, Pan Y (2016) The preoperative platelet-lymphocyte ratio versus neutrophil-Lymphocyte ratio: which is better as a prognostic factor in oral squamous cell carcinoma? TherAdv Med Oncol 8(3):160–167
11. Kum RO, Ozcan M, Baklacı D (2014) Elevated neutrophil-to lymphocyte ratio in squamous cell carcinoma of larynx compared to benign and precancerous laryngeal lesions. Asian Pac J Cancer Prev 15:7351–7355
12. Kara M, Uysal S, Altinisik U, Cevizci S, Guclu O, Derekoy FS. The pre-treatment neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and red cell distribution width predict prognosis in patients with laryngeal carcinoma. Eur Arch Otorhinolaryngol. 2017; 274 (1): 535-542.

13. Tangthongkum M, Tiyanuchit S, Kirtsreesakul V, Supanimitjaroenporn P, Sinkitjaroenchai W. Platelet to lymphocyte ratio and red cell distribution width as prognostic factors for survival and recurrence in patients with oral cancer. Eur Arch Otorhinolaryngol. 2017; 274 (11): 3985-3992.
14. Malik A, Mishra A, Mair M, Chakrabarti S, Garg A, Singhvi H, et al. Role of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio as prognostic markers in oral cavity cancers. Indian J Med PaediatrOncol2019; 40:94-100
15. Dumitru CA, Lang S, Brandau S. Modulation of neutrophil granulocytes in the tumor microenvironment: Mechanisms and consequences for tumor progression. Semin Cancer Biol2013; 23:141-8.
16. Motomura T, Shirabe K, Mano Y, Muto J, Toshima T, Umemoto Y, et al.Neutrophil–lymphocyte ratio reflects hepatocellular carcinoma recurrence after liver transplantation via inflammatory microenvironment. Journal of Hepatology 2013;58(1):58–64.
17. Kantola T, Klintrup K, Vayrynen JP, Vornanen J, Bloigu R, Karhu T, et al. stage-dependent alterations of the serum cytokine pattern in colorectal carcinoma. British Journal of Cancer 2012;107(10): 1729–36.
18. Sabrkhany S, Griffioen AW, Oude Egbrink MG (2011) The role of blood platelets in tumor angiogenesis. BiochimBiophysActa 1815(2):189–196
19. Egan K, Crowley D, Smyth P, O'Toole S, Spillane C, Martin C et al (2011) Platelet adhesion and degranulation induce pro-survival and pro-angiogenic signalling in ovarian cancer cells. PLoS One 6(10): e26125.
20. Dunn GP, Old LJ, Schreiber RD (2004) The immunobiology of cancer immunosurveillance and immunoediting. Immunity 21:137–148.
21. Semba RD, Patel KV, Ferrucci L, Sun K, Roy CN, Guralnik JM, et al. Serum antioxidants and inflammation predict red cell distribution width in older women: The Women's Health and Aging Study I. ClinNutr. 2010; 29: 600-4
22. Nemeth E, Rivera S, Gabayan V, Keller C, Taudorf S, Pedersen BK, et al. IL-6 mediates hypoferremia of inflammation by inducing the synthesis of the iron regulatory hormone hepcidin. The Journal of clinical investigation. 2004; 113: 1271-6

How to cite this article: Aathira TS, Gupta S, Krishnan AS et.al. Blood parameters as surrogate markers to predict treatment response after radiation therapy in head and neck malignancies. International Journal of Research and Review. 2020; 7(2): 173-178.

******