DOI: 10.7860/JCDR/2025/78703.21271

Original Article

Oncology Section

Investigating the Predictive Value of Neutrophil to Lymphocyte Ratio on Radiation Therapy Outcomes: A Cohort Study

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ABSTRACT

Introduction: The gold standard in the management of locally advanced cervical cancer is definitive chemoradiation followed by brachytherapy. Nonetheless, the interdependence of radiation response and immune balance in cancers is debatable. Inflammation markers such as C-Reactive Protein (CRP) and Pro-B-type Natriuretic Peptide (Pro-BNP) have established prognostic value in cancers, but the Neutrophil-Lymphocyte Ratio (NLR) is gaining prominence due to its easy accessibility and strong predictive role in malignancies such as lung, pancreatic and gastric cancers.

Aim: To study NLR as a predictor of clinical response to radiation in cervical cancer.

Materials and Methods: This cohort study assessed 60 women from a tertiary cancer hospital in Western Uttar Pradesh, catering to many districts in North India, between August 2017 and July 2019. The routine blood investigations during assessment at baseline and NLR were obtained. Pelvic chemoradiation of 50 Gy in 25 fractions was administered over 5 weeks with weekly concomitant cisplatin at 35 mg/m^2. Tumour response was evaluated and statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 23.0 to find the association between NLR and Complete Response (CR).

Results: Clinical CR was noted in 44 (73.3%) of participants. In the CR group, 10 (22.7%) had baseline haemoglobin levels below 13 g/dL compared to 13 (81.25%) in the Partial Response (PR) group. The majority of patients (39/44) with CRs were noted at NLR levels below 2.9. When the NLR (cut-off 2.9) and response (Complete and PR; CR and PR) were evaluated, the p-value was reported as 0.06, which, although not statistically significant, is encouraging for further investigation towards consensus.

Conclusion: These observations suggest that inflammation appreciably influences the intrinsic tumour characteristics in patients with cervical cancer. Hence, the utility of NLR as a marker to categorise the risk of recurrence in patients with cervical cancer presents an intriguing concern for the future.

Keywords: Cervical cancer, Chemoradiation, North India, Predictive value

INTRODUCTION

The key characteristic of the tumour microenvironment that plays a central role in the initiation, promotion, progression, invasion and metastasis of a tumour is inflammation [1]. Systemic inflammation has various markers; for example, serum CRP, Pro-BNP and precalcitonin, and the prognostic and predictive values of these have already been established for numerous malignant tumours [2]. In recent times, blood-based markers of inflammation which are easily calculated in a hospital setting, such as the NLR, Platelet/Lymphocyte Ratio (PLR) and Red Cell Distribution Width (RDW), have become appealing due to their ease of availability and predictive and prognostic value for assessing various cancers, including non small cell lung cancer, pancreatic adenocarcinoma, gastric cancer and renal cell carcinoma [2].

Haematological parameters such as NLR, PLR and RDW have emerged as significant prognostic markers in patients undergoing Radiotherapy (RT). Elevated pretreatment NLR and PLR are often associated with poorer outcomes, as they reflect systemic inflammation and immune dysregulation, which can influence tumour progression and treatment resistance. In cervical cancer, elevated NLR and PLR have been correlated with lymph node metastasis and worse survival, although RDW has shown mixed results depending on the study. Post-RT, changes in NLR, PLR and RDW can indicate treatment response and long-term prognosis. Hence, their practicality for managing cervical cancer remains crucial. These haematological indices offer valuable insights into both pretreatment risk assessment and post-treatment monitoring, though their interpretation should be context-specific and integrated with other clinical factors.

Therefore, this study aimed to evaluate the role of NLR in cervical cancer, so that this simple and affordable investigation, derived from routine Complete Blood Count (CBC), can be used to prognosticate one of the most common cancers in a developing country like India.

MATERIALS AND METHODS

This clinical cohort study of women with cervical cancer was conducted over two years, from August 2017 to July 2019, at a tertiary care centre in Western Uttar Pradesh, catering to many adjoining districts of Uttar Pradesh, North India. The study was conducted by the Department of Radiation Oncology after obtaining clearance from the Institute Ethics Committee, Faculty of Medicine, at the lead author's university (Ref. 17.07.2017/646/FM). Written informed consent was obtained from patients in accordance with the Helsinki Declaration.

Inclusion criteria: Patients with histologically confirmed carcinoma of the cervix (FIGO stage IB to IVA) referred for radiation therapy, age ≥18 years, Karnofsky Performance Status (KPS) of >60%, optimum haematologic parameters (Haemoglobin (Hb) >10 g/dL, White Blood Cells (WBC) >4,000/L and platelets >100,000/L), renal function test (serum creatinine <1.4 mg/dL), liver function test (serum bilirubin <1 mg/dL) were included in the study.

Exclusion criteria: Patients who refused to give consent, with serious co-morbidities, patients with distant metastasis, pregnant or breastfeeding mothers, prior surgery, chemotherapy, or radiotherapy for the same disease were excluded form the study.

Treatment protocol: Patients received External Beam Radiotherapy (EBRT) using a Telecobalt 60 unit, delivering 50 Gy in 25 fractions to the pelvis, with concurrent cisplatin at 35 mg/m^2 weekly. Routine investigations (CBC, RFT and LFT) were performed and baseline NLR was calculated and noted; if necessary, supportive management was provided. After one week of completing EBRT, patients received

three fractions of high-dose-rate intracavitary brachytherapy of 8 Gy each, administered a week apart. The Microselectron HDR was used with a source of Iridium-192 with a nominal activity of 10 curies. A total of three fractions of brachytherapy at 8 Gy per fraction were delivered to Point A.

Work-up protocol: Acute haematological toxicity was monitored weekly during treatment. Patient symptoms such as diarrhoea, vomiting and dysuria were reported according to Radiation Therapy Oncology Group (RTOG) criteria [3].

Response assessment protocol: As per RTOG criteria, adverse reactions were validated and toxicity was scored. Patients were examined after the completion of radiotherapy and then at 6 to 8 weeks, followed by assessments at three months and six months, and then three-monthly throughout the study period.

Outcome protocol: Clinical outcomes were assessed during follow-up by clinical examination (per vaginal) and necessary investigations as indicated. After the completion of treatment, all patients were evaluated for response CR, PR and acute toxicity. The response was evaluated three months after the end of radiotherapy through clinical and radiological examination {per vaginal and Magnetic Resonance Imaging (MRI) pelvis}. Logistic regression was performed to find the association between the two variables, namely NLR and CR. Receiver operating characteristics were analysed and a cut-off NLR value of 2.9 was found to have the highest specificity and sensitivity in predicting CR. The results of both arms were compared in terms of NLR <2.9, = 2.9 and >2.9.

STATISTICAL ANALYSIS

Data were analysed using SPSS version 23.0 (Inc., Chicago, IL, USA). The data were summarised in the form of proportions and frequency tables for categorical variables. Continuous variables were summarised using means and standard deviations. The Chi-square test was used to analyse the association between various variables. A p-value<0.05 was considered statistically significant.

RESULTS

The median age at presentation was 49 years (range 41 to 51 years) [Table/Fig-1].

Socio-demographic characterstics	n (%)
Median age (years)	49
Menstrual profile	
Premenopausal	30 (50)
Postmenopausal	30 (50)
Residence profile	
Urban	26 (43.3)
Rural	34 (56.7)
Socio-economic status	
Lower	16 (26.7)
Lower middle	20 (33.3)
Middle	16 (26.7)
Upper	8 (13.3)
Parity	
Nulliparous	2 (3.3)
Multiparous	58 (96.7)

[Table/Fig-1]: Baseline characteristics of study population.

Clinical CR was noted in 44 (73.3%) patients. In the group achieving clinical CR, 10 (22.7%) patients had baseline haemoglobin levels below 13 g/dL, as opposed to 3 (18.75%) patients in the partial responders group. Of the women achieving CR, 8 (18.2%) had symptomatic pelvic inflammatory disease at presentation that required antibiotics. In contrast, pelvic inflammatory disease at baseline was recorded in 3 (18.75%) patients who failed to achieve CR [Table/Fig-2].

Variables	Complete Response (CR) (n=44) n (%)	Partial Response (PR) (n=16) n (%)
Stages		
IBI	3 (6.8)	1 (6.25)
IB2	2 (4.5)	1 (6.25)
IIA	5 (11.4)	3 (18.75)
IIB	20 (45.5)	7 (43.75)
IIIA	6 (13.6)	2 (12.5)
IIIB	7 (15.9)	2 (12.5)
IVA	1 (2.3)	0
Haemoglobin		
<13 g/dL	10 (22.7)	3 (18.75)
>13 g/dL	34 (77.3)	13 (81.25)
Pelvic Inflammatory Disease (PID) at baseline		
Symptomatic	8 (18.2)	3 (18.75)
Asymptomatic	36 (81.8)	13 (81.25)
NLR		
<2.9	39 (88.6)	0
=2.9	5 (11.4)	5 (31.25)
>2.9	0	11 (68.75)

[Table/Fig-2]: Chemoradiation response.

Out of the 44 patients who achieved CR, 39 (88.6%) were noted to have NLR levels below 2.9 [Table/Fig-3]. Similarly, out of the 16 patients with PR to chemoradiation, 5 (31.2%) had NLR=2.9, while the remaining 11 (~70%) had NLR>2.9. When the NLR (cut-off at 2.9) and response (complete and partial; CR and PR) were evaluated, the p-value was 0.06, which, although not statistically significant, is encouraging for further studies investigating the predictive value of NLR.

Patient characteristics	NLR <2.9 (n=39)	NLR=2.9 (n=10)	NLR >2.9 (n=11)
Median age (years)	42	50	51
FIGO stage (2009)			
IB1	1	3	0
IB2	3	0	0
IIA	5	2	1
IIB	23	2	2
IIIA	6	1	1
IIIB	0	2	7
IVA	1	0	0

[Table/Fig-3]: Characteristics of study population according to NLR values.

Logistic regression output analysis, along with Haldane-Anscombe correction, demonstrated a significant association of NLR with CR following chemoradiation, with NLR≥2.9 being associated with 99.6% lower odds of CR compared to NLR<2.9 (p-value<0.001). It was also calculated that there are 238-fold lower odds of response if NLR≥2.9. The overall model fit was good (Hosmer & Lemeshow test p-value>0.05) [Table/Fig-4].

NLR	Complete Response (CR) (n=44)	Partial Response (PR) (n=16)
<2.9	39	0
=2.9	5	5
>2.9	0	11

[Table/Fig-4]: Logistic regression output.

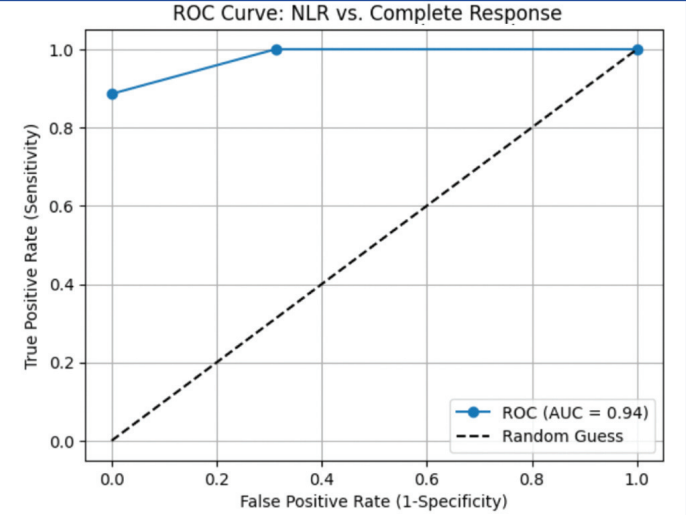
For Receiver Operating Characteristic (ROC) analysis, CR was considered the positive class and PR the negative class. The following coordinates were used for plotting the ROC curve [Table/Fig-5]:

- (0, 0.886) → NLR <2.9
- (0.312, 1.0) → NLR ≤2.9
- (1.0, 1.0) → All patients

NLR threshold	Sensitivity (TPR)	1-Specificity (FPR)
<2.9	39/44=88.6%	0/16=0%
≤2.9	(39+5)/44=100%	(0+5)/16=31.2%
All	100%	100%

[Table/Fig-5]: ROC analysis.

ROC curve analysis of NLR demonstrated an optimal cut-off value of 2.9 (p-value <0.001, sensitivity 88.6, specificity 100). The area under the ROC curve shows excellent discrimination at 0.94 for distinguishing between CR and PR [Table/Fig-6].



[Table/Fig-6]: ROC curve.

DISCUSSION

A review of studies has shown the important role of inflammation in the genesis, maturation and spread of cancer [1,2,4,5]. Neutrophils are thought to be the principal source of circulating Vascular Endothelial Growth Factor (VEGF), which play a critical role in tumour-associated angiogenesis by producing various inflammatory cytokines, such as Tumour necrosis factor (TNF) and interleukin 1, thereby creating a conducive microenvironment for tumours [1]. In a meta-analysis by Huang QT et al., the results indicated that the NLR was unequivocally related to tumour size and significantly correlated with lymph node involvement as well as advanced tumour stage (FIGO) [6]. These observations suggest that the severity of inflammation might markedly affect inherent tumour characteristics in patients with cervical cancer.

Conversely, lymphocytes play a significant role in the cancer-specific immune response [2]. It has been shown that an increased infiltration of lymphocytes into tumour tissue correlates with better prognosis. NLR serves as a marker for gauging the systemic balance between neutrophil-dependent protumour inflammation and lymphocyte-associated antitumour immune response [7,8]. An elevated NLR could indicate a trend towards increased protumour inflammation and decreased antitumour immune capacity.

Yodying H et al., assessed the prognostic role of NLR in oesophageal cancer and indicated that NLR was linked with tumour invasion and lymph node metastasis [9]. Meanwhile, Xue TC et al., found that NLR was associated with vascular invasion in hepatic carcinoma [10]. In a study conducted by Lee YY et al., poor survival outcomes were observed in the high NLR group (>1.9) in comparison to the lower NLR group (<1.9) [11]. In a recent study by Wu J et al., it was shown that patients with higher NLR were younger in age, had larger tumour sizes, advanced clinical stage and positive lymph node metastasis [12]. Present study results similarly demonstrated that NLR was positively related to tumour size and significantly correlated with lymph node involvement as well as advanced tumour stage (FIGO). These findings indicate that inflammation may substantially influence inherent tumour characteristics in patients with cervical cancer. In fact, good nutritional status and low systemic inflammation at pretreatment were linked to longer progression-free survival and overall survival [13].

Results from present study reveal that higher baseline NLR values were associated with poor CR to chemoradiation, establishing a significant association between NLR, a marker of the patient's immune and inflammatory response and clinical radiation response. These findings suggest that lower baseline NLR values in patients with locally advanced cervical cancers are more favourable and likely to lead to clinical CR after chemoradiation. High NLR (>3.1) was found to be linked to PR in three-quarters of the study population in a study conducted at TMC Kolkata in 2019 by Gangopadhyay A [14]. Likewise, high NLR (cut-off at 3) was associated with worse survival outcomes in cervical cancer patients [15]. These results resonate with present study, where the cut-off for NLR was 2.9. Aggregated data from a meta-analysis involving over 19,000 patients reiterated that those with increased NLR prior to treatment exhibit decreased overall survival and reduced progression-free survival, also impacting the incidence of distant metastasis [16]. NLR is a prognostic marker that is easily accessible in the treatment setting, as it can be estimated through a standard haemogram.

Limitation(s)

A smaller number of patients and a shorter follow-up period were possible limitations of the study. It is suggested that a longer follow-up and increased recruitment of patients be conducted to draw definitive conclusions.

CONCLUSION(S)

The NLR is an easily accessible biomarker, as it can be obtained from a routine investigation, namely a haemogram. This is particularly significant in developing countries, where cervical cancer continues to be a considerable burden on public health resources. Therefore, its use as a marker to categorise the risk of recurrence in patients with cervical cancer warrants further research.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Feb 19, 2025
- Manual Googling: May 09, 2025
- iThenticate Software: May 27, 2025 (6%)

ETYMOLOGY: Author Origin

EMENDATIONS: 7

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Feb 18, 2025**
Date of Peer Review: **Mar 20, 2025**
Date of Acceptance: **May 29, 2025**
Date of Publishing: **Jul 01, 2025**