Higher Neutrophil to Lymphocyte Ratio (NLR) is Significant Predictor of Higher Gleason Scores Among Cases of Prostate Cancer

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ABSTRACT

Introduction: Cancer development is significantly influenced by chronic inflammation. The inflammatory indices NLR and PLR have also been proposed as a new indicator of tumour necrosis, hypoxia, and systemic inflammation. However, there is little information on NLR and PLR's predictive significance in prostate cancer. Hence, this study conducted to assess the effect of preoperative NLR and PLR levels among histologically confirmed cases of prostate carcinoma using the Gleason scoring system.

Methodology: A retrospective study conducted among 117 biopsy-proven prostate cancer cases who had a radical prostatectomy at various hospitals in Western India. Information on age of the patients, pre operative PSA value, and complete blood count (CBC) measured before to surgery. The radical prostatectomy specimens' tumour grade was evaluated using the Gleason grading. The relationship between the NLR, PLR, and Gleason score was examined using logistic regression analysis.

Results: Total 72 patients had low grade tumours (Gleason $\leq$ 7), while 45 patients had high grade tumours (Gleason $\geq$ 7). When blood PSA levels were compared, the high-grade group had statistically substantially higher values than the low-grade group (p=0.023; Table 2), according to the results. Age adjusted analysis revealed that Ln-NLR (p=0.021) was significantly linked with high-grade prostate cancer while Ln-PSA [p=0.051] and Ln-PLR [p=0.065] were poorly linked with gradin god prostate cancer.

Conclusion: This study concluded that elevated NLR levels are an important clinical marker for individuals with high-grade prostate cancer. In order to verify our findings with specific cut-off levels of various inflammatory markers, more large-scale follow-up investigations are required.

Keywords: Prostate Carcinoma, LNR, PNR, Gleason Score, PSA

INTRODUCTION

Prostate cancer is primarily a disease of the elderly with more than three quarter of the cases occurring in men above 65 years of age. However, this disease has become a major health problem globally during and become the second most frequently diagnosed cancer in men worldwide and the fifth most common cancer overall.(1)

With aging and an increased use of the PSA as a screening marker, there has been a substantial increase in the prostate cancer diagnosis documented in many countries (2). In India, oral and esophageal cancers have the highest incidence, whereas rectal, prostate, and lung cancers have the lowest.(3, 4) Although the cancers rate in India are lower than those seen in Western countries, increase in life expectancy and changes in lifestyles increase the rates of cancers in this country, particularly prostate cancer.

Cancer development is significantly influenced by chronic inflammation (5). Age, genetics, and a Western lifestyle are the classic risk factors for prostate cancer (5). Prostate cancer etiopathogenesis involves environmental variables that cause persistent prostate inflammation in addition to genetic factors, such as infection, nutrition, or other exposures (5).

Furthermore, angiogenesis and the epithelial-mesenchymal transition (EMT), which affect the dynamics of the tumour microenvironment in prostate cancer, are significantly influenced by chronic inflammation.(6)

A regular complete blood count may readily measure the inflammatory indices neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), which have been shown to have predictive significance in solid organ malignancies (7, 8). They have also been proposed as a new indicator of tumour necrosis, hypoxia, and systemic inflammation. These fundamental clinical criteria have been used in several papers to show how to distinguish between malignant and benign prostate tumours (9, 10). However, there is little information on NLR and PLR's predictive significance in prostate cancer. Hence, in this study, our objective was to study the effect of preoperative NLR and PLR levels among histologically confirmed cases of prostate carcinoma using the Gleason scoring system.

MATERIALS AND METHODS

Men who were diagnosed with biopsy-proven prostate cancer and had a radical prostatectomy between October 2019 and January 2023 at various hospitals in Western India were included in this retrospective analysis. Six hospitals in all took part in the study and contributed data on 117 qualifying cases of prostate cancer. Patients with inflammatory or infectious diseases were not included, nor were those without adequate medical records. Additionally, before surgery, none of the patients got anticancer treatment. The study protocol has been approved by the institutional review board of the Godhara GMERS Medical College and Hospital located in Gujarat. Informed written consent was obtained from all the participants before initiation of data collection.

A questionnaire was developed with the consultation of senior faculties from surgery and pathology department from the institute. The questionnaire was pilot tested for feasibility. Information on age of the patients and pre operative PSA value was recorded. The complete blood count (CBC) measured before to surgery (baseline) was used to compute the neutrophil and lymphocyte counts for the NLR, and the platelet count divided by the lymphocyte count was used to calculate the PLR. The same surgical methods were used in each surgery. The radical prostatectomy specimens' tumour grade was evaluated using the Gleason grading recommended by the International Society of Urological Pathology (ISUP) (11). Presence of lymph node metastasis and status of resection margin was also recorded.

Statistical Analysis

According to the distributions, continuous data were shown as the mean SD or median (interquartile range), and categorical variables were shown as frequencies and percentages. According to normality, the variables were compared between the two groups using the t-test or Mann-Whitney U test for continuous variables and the Chi-squared test for categorical data. The relationship between the NLR, PLR, and Gleason score was examined using logistic regression analysis. To achieve a normal distribution, all leukocyte, neutrophil, lymphocyte, platelet, PSA, NLR, and PLR variables were log transformed; the transformed values were then employed in the regression analysis. Multiple analyses were aged-adjusted since it was unable to collect the body mass index data for all patients. The model did not group independent variables together to account for potential interaction. For the analysis, the Gleason score values were divided into low grade and high grade groups. Statistical significance was defined as a p-value 0.05. The Statistical programme for social sciences, version 25.0 (IBM SPSS Corp.; Armonk, NY, USA) was used to conduct the statistical analysis.

RESULTS

This study included 117 men with histologically confirmed prostate carcinoma. The demographics of study population are described in Table 1. The mean age of the patients was 61.2 (sd 7.1) years, with the median preoperative Prostate Specific Antigen (PSA) of 7.9 (4.9, 15.8) ng/mL. The pathology report on the surgical specimens revealed that 72 patients had low grade tumours (Gleason < 7), while 45 patients had high grade tumours (Gleason more than 7). All patients had radical prostatectomy. Lymph node metastases was limited to six cases. 28 patients (24%) out of 117 got a favourable resection margin.

Table 1. Clinical and laboratory profile of patients included in the study

Characteristics	**Values (n=117)**
Age of patients (years, mean±SD)	61.2±7.1
Postate Specific Antigen (ng/mL, median IQR)	7.9 (4.9, 15.8)
Gleason Score (cases, %)	
Low Grade	72 (615%)
High Grade	45 (38.5%)
Lymph node metastasis (cases, %)	6 (5.1%)
Positive resection margin (cases, %)	28 (23.9%)
Hemoglobin (g/dL, mean±SD)	13.9±1.3
Neutrophil (per µL, median, IQR)	4360 (3710, 5920)
Leukocyte (per µL, median, IQR)	7390 (6270, 8850)
Platelet (per µL, median, IQR)	253000 (180000, 274000)
Lymphocyte (per µL, median, IQR)	2080 (1770, 2550)
NLR (median, IQR)	2.1 (1.7, 2.8)
PLR (median, IQR)	103.5 (82.2, 136.3)

PSA: prostate specific antigen; SD: standard deviation; IQR: interquartile range; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio

According to Table 1, the median leukocyte level was 7390 (6270, 8850), and the PLR was 103.5 (82.2, 136.3). Additionally, we analysed every attribute across the study subgroups that were given low and high grades based on the Gleason scoring method. In Table 2, the comparative analysis is shown. When blood PSA levels were compared, the high-grade group had statistically substantially higher values than the low-grade group (p=0.023; Table 2), according to the results. Despite the fact that both the NLR and PLR values were greater in the high-grade group, the difference in NLR (p=0.058) and PLR (p=0.211) were statistically non-significant.

Table 2. Bivariate analysis of variables of cases with high and low Gleason score

Variables	**High Grade [Gleason ≥7] (n=45)**	**Low Grade [Gleason≤ 7] (n=72)**	**P value**
Age (years, mean±SD)	62.0±6.2	60.1 ± 5.0	0.071
PSA (ng/mL, median IQR)	11.0 (6.4, 32.1)	6.7 (4.9, 12.0)	0.023
Lymph node metastasis (n, %)	6 (13.3%)	0 (0%)	<0.001
Positive resection margin (n, %)	15 (33.3%)	12 (16.7%)	0.037
Hemoglobin (g/dL, mean ± SD)	14.1 ± 1.1	13.7 ± 1.3	0.089
Neutrophil (/ µL, median, IQR)	4660 (3610, 5990)	4290 (3860, 5790)	0.646
Leukocyte (/ µL, median, IQR)	7240 (6320, 8750)	7470 (6352, 8767)	0.772
Platelet (/ µL, median, IQR)	216000 (201000, 247000)	278000 (188000, 271000)	0.527
Lymphocyte (/ µL, median, IQR)	2110 (1720, 2437)	2050 (1822, 2663)	0.392
NLR (median, IQR)	2.5 (1.7 3.2)	2.04 (1.5, 2.7)	0.058
PLR (median , IQR)	108 (87, 146)	101 (79, 125)	0.211

PSA: prostate specific antigen; SD: standard deviation; IQR: interquartile range; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio

Association Between the NLR, PLR, and Gleason Score

A univariate logistic regression analysis revealed a statistically significant relationship between the levels of Ln-PSA (OR 1.79, 95% confidence interval [CI] [1.05, 2.9] p=0.018), Ln-lymphocyte (OR 0.43, 95% CI [0.18, 0.98] p=0.035), and Ln-NLR (1.84, 95%CI [OR 1.16, 3.72] p=0.014) and a high Gleason score. However, the Ln-PLR levels showed a marginally statistically significant correlation (OR 2.15, 95% CI (0.86, 5.04), p=0.053). Age adjusted analysis of all these variables revealed that Ln-NLR (aOR 1.83, 95% CI [1.09, 3.26] p=0.021) still statistically significantly linked with high-grade prostate cancer. Age adjusted analysis showed a weak correlation for Ln-PSA [1.80, 95% CI (aOR 0.97, 2.98) p=0.051] and Ln-PLR [2.21, 95% CI (aOR 0.89, 4.28) p=0.065].

Table 3. Bivariate and Age adjusted Multiple analysis of log scale of variables between cases with high and low Gleason score

Variables	OR (95% CI)	p value	aOR (95% CI)*	p value
Age (years, mean±SD)	1.04 (0.99, 1.10)	0.071	-	
Ln-PSA (ng/mL, median IQR)	1.79 (1.05, 2.9)	0.018	1.80 (0.97, 2.98)	0.051
Ln-Neutrophil (/µL, median, IQR)	1.63(0.54, 2.73)	0.426	1.38 (0.66, 2.75)	0.348
Ln-Leukocyte (/µL, median, IQR)	0.89 (0.39, 1.85)	0.739	0.87 (0.44, 2.02)	0.781
Ln-Platelet (/µL, median, IQR)	1.11 (0.29, 2.97)	0.842	1.09 (0.27, 3.17)	0.802
Ln-Lymphocyte (/µL, median, IQR)	0.43 (0.18, 0.98)	0.035	0.37 (0.14, 0.89)	0.042
Ln-NLR (median, IQR)	1.84 (1.16, 3.72)	0.014	1.83 (1.09, 3.26)	0.021
Ln-PLR (median, IQR)	2.15 (0.86, 5.04)	0.053	2.21 (0.89, 4.28)	0.065

*Age adjusted multiple analyses. PSA: prostate specific antigen; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; Ln: log transformed

DISCUSSION

Recently, a number of studies were conducted with the goal of identifying criteria that would be affordable, conveniently accessible, and useful in clinical application for the diagnosis, follow-

up, and prognosis prediction of solid organ tumours. Men who have a prostate cancer suspicion typically get a prostate biopsy, a rectal digital examination, and measurement of their serum PSA levels. By doing a trans-rectal prostate biopsy, there is a 20–67% chance of discovering prostate cancer (12) In the initial prostate biopsy, false negative findings have been recorded at a rate as high as 23%.

Repeated biopsies are known to be necessary in the detection of cancer, particularly in individuals whose prior pathology reports indicated an abnormal small acinar proliferation or high-grade prostate intraepithelial neoplasia (13, 14). As a result, numerous procedures, including magnetic resonance imaging, have been developed to clarify the diagnosis before performing a biopsy. These tests, however, are costly and difficult to carry out. As a result, all research has been concentrated on creating markers that are less expensive and simpler to utilise in clinical settings.

By immune cell infiltration in prostate tissue, fibroblast activation, and other processes, inflammation is essential for prostatic carcinogenesis and tumour growth (5, 15) One CBC can examine the NLR ratio and PLR at normal clinic visits; these are affordable and useful measures. The NLR has been investigated in a number of distinct solid organ tumour regions (16), and it has been discovered to be predictive for both the development and prognosis of cancer. In our research, we showed that the NLR levels were independent predictors of high-grade prostate cancer in both univariate and multivariate analyses, with approximately the same degree of prediction as blood PSA levels.

Previous investigations discovered the NLR as an independent prognostic factor in prostate cancer, which is consistent with our findings (17) The clinical characteristics of prostate cancer and the Gleason score system are highly correlated (11). A higher score indicates a poorer prognosis for cancer (18). Poor prognosis is associated with poor quality of life in cancer patients. (19, 20) PAs a result, the discovery of a strong correlation between high NLR levels and high Gleason scores points to the utility of NLR in predicting high-grade histology in terms of a bad tumour prognosis.

Our findings support those by Lu et al. (21), which show that the Gleason score and malignancy of prostate cancer increase with NLR levels. Similar findings have also been reported by Langsenlehner et al. (22), who showed that a high NLR is linked to prostate carcinogenesis and came to the conclusion that tumour response linked to a low lymphocyte count and inflammation linked to an elevated neutrophil count may both contribute to carcinogenesis.

In a study including 2067 prostate cancer patients, Jang et al. (23) found that greater NLR levels attained before to radical prostatectomy are linked to worse survival and a higher risk of biochemical recurrence. In light of the aforementioned large, multicenter validation studies that would evaluate the NLR cut-off level in the prediction of grading prostate carcinoma, the NLR would be used as an affordable, accessible, and promising marker for assessing the cancer clinical behaviour in these patients.

The PLR measure, which is also available from the CBC, is the other straightforward inflammation-based metric that we evaluated. Numerous investigations shown that the poor prognosis related with increased pretreatment PLR levels in numerous forms of solid tumours (24, 25). Although the patients in our research tended to have significantly higher PLR levels and the regression analysis indicated a positive correlation with the Gleason score, we were unable to detect a statistically significant link between the two variables.

There are contradictory findings in the literature about the predictive utility of PLR for the diagnosis and prognosis of prostate cancer. According to Yuksel et al. (10), the PLR is an additional predictive sign for differentiating between benign and malignant prostate tumours. The PLR was recommended by Wang et al. (17) as an additional marker for predicting the prognosis in prostate cancer patients. Another study that examined PLR and NLR levels in conjunction with urological tumours discovered that both inflammatory parameters were connected to a poor prognosis for prostate carcinoma (26).

Evidence suggests that a greater PLR level represents a pro-tumor reaction (elevated platelet-dependent tumour development) and a reduced lymphocyte-mediated anti-tumor immune response, both of which are linked to tumour progression and unfavourable outcomes (15, 22). On the other hand, Zanaty et al. (27) examined the predictive value of preoperative NLR and PLR levels among patients with organ-confined prostate cancer but were unable to find any significant association for either marker, coming to the conclusion that the localised tumours might not cause the systemic inflammatory response.

In our investigation, we also failed to discover a significant correlation between the PLR and Gleason score. It's possible that the tissue level inflammatory pathways and how they manifest in clinical laboratory findings are not always connected. The weak correlation between the PLR and histological state in our study may indicate that neutrophils rather than platelets have a more significant role in the initiation and progression of malignancy. However, investigations that

would evaluate samples of blood and specimens simultaneously should be conducted in order to better clarify this issue.

We think the sample size we used for our research was appropriate. However, the retrospective nature of our study's design may restrict how we may interpret the causality of the findings. A longer follow-up study to establish if there is a correlation with long-term clinical prognosis would yield more accurate and therapeutically useful data.

CONCLUSION

Overall, our research supports the notion that elevated NLR levels are an important clinical marker for individuals with high-grade prostate cancer. Regarding the correlation with PLR levels, we were unable to achieve statistical significance. In order to verify our findings with specific cut-off levels of various inflammatory markers, more large-scale follow-up investigations are required.

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