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Significance of Neutrophil-Lymphocyte Ratio In Prostatic Cancer Patients And Its Association With Total PSA Levels

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Abstract

Background: Neutrophil –Lymphocyte ratio(NLR) is easily available and accessible marker of systemic inflammatory reposnse. In many malignancies, it is considered to be a potential marker for prognosis.

Aim : To determine the significance of NLR in prostatic carcinoma cases and to look for the association with the total prostate specific antigen(PSA) levels.

Materials and methods: A total of 92 histopathologically diagnosedprostatic carcinoma cases were included; data for the calculation of NLR and also total PSA levels were retrieved, reviewed and evaluated retrospectively during a period from January 2018 to October 2022 in a tertiary care hospital.

Results: Neutrophil-Lymphocyte ratio and total PSA levels were compared to the histopathological features like gleason pattern(especially cribriform pattern),Gleason score and Gleason grade using Pearsons correlation and independent t test. NLR and total PSA showed significant correlation statistically with Gleason grade group (r value:0.22,0.277; p value:0.035,0.007).

Conclusion: NLR can be used as an independent biomarker as an adjunct to the total PSA in the early diagnosis of the prostatic carcinoma.

Abbreviations: Prostatic carcinoma(PCa),Gleason score(GS), Neutrophil-lymphocyte ratio(NLR),National comprehensive cancer network(NCCN),Prostate specific antigen(PSA), Transurethral resected prostatic specimens (TURP).

Keywords: Prostatic carcinoma, Neutrophil- lymphocyte ratio, Gleason score and Gleason grade group

Introduction

Prostate cancer (PCa) is the second most common cancer and fifth leading cause of cancer death among men worldwide. In several developed and developing countries, prostate cancer (PCa) has become the most common malignancy among men. PCa having PSA <10ng/ml, stage T1–T2a, and Gleason score (GS) ≤6 by the National Comprehensive Cancer Network (NCCN) guidelines is low risk PCa. Inflammation plays a critical role in the pathogenesis of cancers and is also an important factor in its progression.

Neutrophil-to-lymphocyte ratio (NLR) is one of the useful biomarkers of cancer-related inflammation and is associated with poor prognosis in various cancers. Its role is important in metastatic PCa, where aggressive disease can be predicted by high NLR ratio.[1, 2]

In cancer patients, lymphopenia is responsible for the impaired cell-mediated immunity, while neutrophilia occurs as a response to systemic inflammation. Hence, NLR is suggested as a marker for general immune response to various stress stimuli. NLR is found to be a helpful tool in the prediction of response to treatment. Pretreatment high NLR have been reported as a poor prognostic factor for survival. High NLR prior to prostate biopsy is found to be associated with the presence of PCa and higher Gleason score as well.[1,2]

Materials And Methods:

A cross sectional study was conducted on 92 samples, including transurethral resected prostatic specimens (TURP), prostatic biopsies and radical prostatectomy specimens received over a period of January 2018 to October 2022 in the Department of Pathology of a tertiary Hospital, Mangaluru, Karnataka, India. The H&E slides were reviewed to reassess histopathological features like Gleason's pattern, the Gleason's scoring and grade group. The patient's relevant clinical data like age, total leukocyte count, absolute neutrophil count, absolute lymphocyte count and total PSA before biopsy or surgery were retrieved from the Department application system(Backbone) and the NLR was calculated. The range of total PSA levels was taken 0 - $\geq$100 and NLR with a cut off value of > 2.5. SPSS Version 23.0 was used for data analysis. Chi-Square test was used to find the correlation of NLR and total PSA with Gleason score and grade in prostatic carcinoma patients. Specimens inadequate for histopathological reporting, paraffin blocks with tissue exhaustion and benign prostatic hyperplasia or other inflammatory conditions of prostate were excluded.

Results:

The histologically proven prostatic carcinoma cases were reviewed; the mean age was found to be 69 years. Out of total 92 cases, 47 prostate biopsies, 21 TURP and 24 radical prostatectomies were studied. In this study, the comparison of total PSA and NLR levels between two groups of Gleason score was done(one goup was Gleason score $\leq$6 (n=20) and other group with Gleason score $\geq$7(n=72))(Table 1)).There was no significant correlation seen in the two groups. However, it was found that the age was significantly correlating with two groups of Gleason score (p =0.02). Gleason grade group was increasing with total PSA and NLR, hence showed a significant correlation (p=0.035, p=0.07)(Table 2). Additionally, we looked for a specific histological pattern, cribriform pattern (figure 1,table 3) (presence of pattern (n=55),absence of pattern (n=37))was compared with NLR and total PSA. Eventhough, the total PSA and NLR were increasing with presence of cribriform pattern, no significance was noted between them(p=0.821,p=0.089).

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Figure1: (A):Prostatic carcinoma with cribriform pattern(4x),(B) Prostatic carcinoma in cribriform pattern with intervening fibromuscular stoma(10 x), (C) cribriform pattern (40 x) characterised by solid proliferation of tumour cells with multiple punched out appearance without intervening stroma.

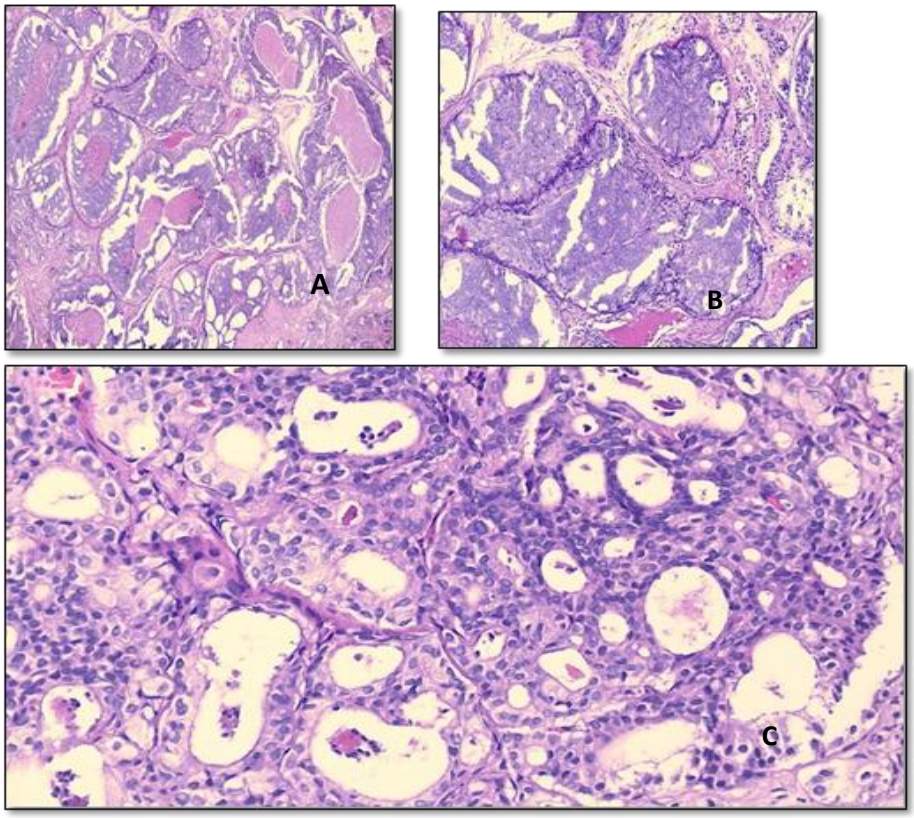

Table 1: Comparison of total PSA and NLR with Gleason score ≤6 and Gleason score≥7

	≤6(n=20)	≥7(n=72)		
	Mean ± SD	Mean ± SD	t	p value
Total PSA (ng/ml)	55.06±33.77	69.87±36.39	-1.635	0.106
NLR	4.67±3.78	6.26±6.83	-0.999	0.321
Age	73.2±5.46	68.26±6.31	3.18	**0.002**

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Table 2: Comparison of Gleason grade group with total PSA and NLR

Parameters correlated with gleason grade(n=92)	correlation(r value)	p value
Total PSA	0.22	**0.035**
NLR	0.277	**0.007**

Table 3: Comparison of total PSA and NLR with cribriform pattern in prostatic carcinomas

	Cribriform pattern present(n=55)	Cribriform pattern absent(n=37)	t –test value	p value
	Mean ± SD	Mean ± SD		
Total PSA	67.35±37.68	65.6±34.31	0.227	0.821
NLR	6.74±7.45	4.69±3.86	1.722	0.089

Discussion:

Prostate cancer is the most common cancer of men in USA and 10th common malignancy in India.[3] Various risk factors like high-sugar and high-calorie diet, smoking, alcohol consumption, sedentary lifestyle, insomnia, androgen level, hereditary and age factors are responsible for the prostatic malignancies in elderly men.[4]Screenings for PCa include serum PSA and digital rectal examination (DRE); biopsy is required to diagnose PCa. The histopathological diagnosis of prostate cancer will only confirm the final diagnosis in most of the cases.[5] Men with 50 years of age or above without any family history of cancer and those at 40 years of age with family history must undergo digital rectal examination (DRE) and serum PSA levels examination annually as recommended by American Urological Association (AUA) and Food and Drug Administration (FDA).[5]

Prostate cancer prognosis and clinical decision-making is ascertained by Gleason score. The Gleason score is entirely based on the classification of adenocarcinoma growth patterns. These patterns are assigned as Gleason grade from 1 to 5. Gleason score is determined by adding together the most common and the highest grade in biopsies, and the two most predominant grades in radical prostatectomy (RP) specimens.[6,7]

Gleason patterns 1–3 encompass well-delineated glandular structures with variable interglandular distances and nodular circumscription with no differences practically and prognostically between these three Gleason patterns, Gleason scores (GS) 2–4 should rarely be diagnosed on biopsy specimens, according to the International Society of Urological Pathology (ISUP) recommendations. Gleason pattern 4 comprises poorly formed, fused, glomeruloid and cribriform glandular structures, whereas Gleason pattern 5 is growth patterns with essentially no glandular differentiation, such as single cells, cords, and solid fields, and the presence of comedonecrosis. Recent studies suggest that these patterns optimize decision making for treatment. Gleason grade group were assigned with help of gleason score. Grade group 1: GS<6,Grade group 2:3+4=7,Grade group 3:4+3=7,Grade group 4:4+4=8,5+3=8,3+5=8,Grade group 5:4+5=9,5+4=9 5+5=10.[6,7]

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PSA is serine protease synthesized in the ductal epithelium and prostatic acini. It is found in normal, hyperplastic and malignant prostate tissue. The most commonly usedcutoff for PSA is 4 ng/mL. If the PSA level is > 10ng/mL, the cancer risk is 67%.[6, 7]

In various carcinomas, progression and development of cancer has been associated with chronic inflammation within the tumor microenvironment[7].In many of the studies, higher incidence of PCa in men were associated with high NLR and PSA values.NLR was also associated with poorer prognosis in patients with prostatic carcinomas.[4] Minardi et al had studied prostatic carcinoma patients with mean age of 65 years, which was nearly same as that of our study. In contrast to our study, they found that NLR was not significantly associated with total PSA, Gleason score and pathological stage.[2] This study suggested a pretreatment evaluation of NLR, because it would help in the increased disease free survival rate in patients with prostatic carcinoma and could be introduced due to its easy availability and low cost,since NLR had shown an increase with recurrence rate. Even though NLR and total PSA were increased with gleason score $\geq$7, this study didn't exhibit a significant correlation with gleason score which showed a similarity with study of Mehmet et al.[1] Wang H et al had found that higher total PSA and NLR were significantly associated with patients with actual GS $\geq$ 7.[9]This discrepancy with our study could be due to interobserver variability in scoring and reduced sample size. The present study tried to reduce this interobserver variability by taking consensus from two senior pathologists in assessing the gleason pattern and gleason scoring, which would give aprécise and accurate reporting. Gleason grade group correlated significantly with NLR and total PSA levels. This difference in significant correlation among gleason score and gleason grade could be due to the assessment of gleason grade group 2(gleason score 3+4), gleason grade group 3(4+3). In the assessment of these two grade groups, there was a huge interobserver variability while reviewing the slides in this study. To avoid this, a consensus was obtained. The cribriform pattern assessment (figure 1) in the prostatic carcinoma was specially done in this study as a two tier scoring(absent or present) because the presence of this pattern is considered to be a poor prognostic factor, due to higher chances of metastases development.[13] The present study showed an increase in PSA and NLR levels with presence of cribriform pattern. So NLR can also be considered as marker in recurrence and metastasis.[1,2,10]

Conclusion: In this era of increasing incidence of carcinomas, inspite of new inventions and ongoing researches in cancer genetics, difficulty still exist in early detection of cancer. The screening modalities should be improvised with utmost importance so that it can lead to early diagnosis and prompt treatment. Hence, NLR can be a novel, cheap and simple, easily accessible marker in many of the carcinomas. However, many drawbacks exist in using this marker as a single independent marker due to its overlapping positivity in inflammatory or benign conditions. Therefore, this study suggests that it can be used as an additional marker in prostatic carcinoma detection irrespective of its measurement along with total PSA levels as a meaningful early detection tool.

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