Ann Med Res 2021;28(5):975-9

Annals of Medical Research

DOI: 10.5455/annalsmedres.2020.09.897

Original Article

Clinical significance of neutrophil-lymphocyte ratio in patients with low-risk prostate cancer

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Abstract

Aim: Active surveillance is a highly emphasized approach to low-risk prostate cancer. Upgrading and upstaging should be evaluated carefully in this strategic management. This study aimed to analyze the relationship of neutrophil-lymphocyte ratio (NLR) with these two clinical conditions.

Materials and Methods: Demographic data, prostate-specific antigen (PSA) levels, prostate volumes, NLR, disease stages, and Gleason scores of 59 low-risk prostate cancer patients who underwent radical prostatectomy and met active surveillance criteria were evaluated in our clinic. The patients were examined in four groups according to their postoperative pathology specimens. Accordingly, the patients with upgrading Group 1, while those without formed Group 2. Similarly, Group 3 consisted of the cases with upstaging and the patients with no upstaging were determined as Group 4.

Results: Median age, PSA levels, prostate volumes, neutrophil and lymphocyte counts of the patients were 69.0 (63.0-72.0) years, 7.24 (5.50-8.90) ng/dL, 65.0 (60.0-65.0) cc, 6.40 (4.87-8.73) K/uL, and 2.50 (1.60-3.10) K/uL, respectively. Prostate volume and age distribution were similar between the groups. PSA levels were higher in Group 1 and Group 3 than those in Group 2 and Group 4 (p=0.012 and p=0.049, respectively). NLR was 3.54 (1.89-5.45) and 1.94 (1.68-3.76) in groups 1 and 2, respectively. Although these values were low in Group 2, a statistically significant relationship could not be established (p=0.266). NLR in groups 3 and 4 was 2.46 (1.52-5.45) and 2.24 (1.68-4.35), respectively. The NLR level in Group 3 was high; however, the difference was not statistically significant (p=0.953).

Conclusion: The study let us to conclude that NLR alone is not sufficient to predict the clinical course of patients with low-risk prostate cancer.

Keywords: Active surveillance; lymphocyte; neutrophil; prostate cancer

INTRODUCTION

Cancers have an important place amongst the reasons that shorten the life span after cardiovascular diseases worldwide. Prostate cancer is the second most common malignancy in men and the fifth leading to death (1). According to 2008 data from our country, the incidence of prostate cancer is 36.3 per 100,000 people (2). It is predicted that 191,930 new prostate cancers will be diagnosed and 33,330 deaths due to this cancer will occur in the United States in 2020 (3). There is an increase in the incidence of prostate cancer in our century as a result of the increasing living standards and prolonged lifetimes of societies. However, prostate cancer patients are diagnosed at an earlier stage in connection with the widespread use of screening tools and the increased awareness of patients. Recent large series of autopsy studies reported that almost half of men over the age of 50 have prostate cancer, and most of these cancers may be less than 0.5 cm, low grade, and clinically insignificant (4). All these data constitute the opinion that it is critical to categorize patients diagnosed with prostate cancer as a whole to determine the treatment strategies effectively. In this context, the recent focus of urology authors is on the concept of low-risk prostate cancer. It is defined as prostate-specific antigen (PSA) < 10 ng/mL, Gleason scores ≤ 6, clinical-stage ≤ T2a, positive cores ≤ 2, and cancer involvement ≤ 50% in each positive core (5). The clinical importance of this patient group is that there is an option of active surveillance in addition to curative treatment options in the treatment strategies. Radiotherapy and radical prostatectomy are the options of curative treatment in low-risk prostate cancer cases. However, these approaches may cause morbidity and

Received: 01.09.2020 **Accepted:** 22.10.2021 **Available online:** 21.05.2021
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functional disorders such as incontinence, and sexual dysfunction. Active surveillance is based on regular PSA measurements, digital rectal examination, and repeated prostate biopsies. The main goal of this approach is to preserve the chance of curative treatment and have the least effect on their quality of life. Several previous studies reported that approximately one in four patients with low-risk prostate cancer who underwent radical prostatectomy had upgrading. This led the researchers to search for new indicators among the active surveillance criteria (6). In this century, many studies have started to position the link between cancer and inflammation. Thus, analyses examining the clinical progression of inflammatory parameters and cancer cells have become extremely important. Although inflammation is a natural process that the organism gives to environmental stimuli, it can cause cancer as a result of its becoming chronic. Inflammatory cells contribute to migration by inducing the proliferation of tumor cells in the neoplastic process and prevent their apoptosis in the tumor cell (7). Changes in the number and rate of inflammatory cells in the blood are monitored during these reactions. One of these changes occurs at the neutrophil-lymphocyte ratio (NLR). This rate increases with systemic inflammation as a result of increasing neutrophil count and decreasing lymphocyte count (5). Although our study has the option of active surveillance, we aimed to evaluate the clinical significance of NLR in predicting post-operative disease upgrading and upstaging in cases with low-risk prostate cancer undergoing radical prostatectomy.

MATERIALS and METHODS

This study retrospectively analyzes patient records of those who underwent open retropubic radical prostatectomy in the our urology clinic between January 2011 and May 2020. It was carried out following the principles of the Helsinki Declaration and with the approval of the local ethics committee (Tokat Gaziosmanpasa University, Ethics Committee, Confirmation number: 20-KAEK-211). The patients' ages, PSA levels, and prostate volumes were noted preoperatively. Digital rectal exam findings and prostate biopsy specimens obtained with transrectal ultrasonography were analyzed. Their clinical stages, Gleason scores, and positive core percentages were determined accordingly. The results of routine blood testing performed before the prostate biopsy were evaluated and NLR was calculated for each patient by dividing the neutrophil count by the lymphocyte count. Hemogram parameters were examined in a biochemistry device with regular maintenance and control (Mindray BC-6800, China). The study only included low-risk prostate cancer cases suitable for active surveillance. The active surveillance criteria were determined as PSA <10 ng/mL, Gleason score ≤6, clinical-stage ≤T2a, positive cores ≤ 2, and cancer involvement ≤50% in each positive core (5,8). Each patient suitable for active surveillance criteria was informed in detail about all the treatment options before radical prostatectomy, and surgical consent was obtained. Radical prostatectomy specimens were analyzed by two different specialists from the department of pathology. After the examination, a Gleason score of ≥ 7 was defined as Gleason score upgrading. Those with Gleason score upgrading were involved in Group 1, and those without in Group 2. Similarly, the tumor stage of ≥T3 was indicative of disease upstaging (9). The patients with disease upstaging were taken into Group 3 and those without into Group 4. The groups were subjected to a statistical analysis among themselves for age, PSA, prostate volume, and NLR. The study did not include cases with a clinical status that would alter NLR such as secondary malignancy, immunological disorder, severe endocrinological pathology, active urinary tract infection, hematological diseases, and the use of anticoagulants or antiaggregants.

Statistical Analysis

Analyses were performed using commercial software (IBM SPSS Statistics 19, SPSS inc., an IBM Co., Somers, NY). Descriptive analyses were performed to provide information on general characteristics of the study population. The variables were presented as the median (Q1-Q3) (Q1: The first quartile of datas (%25); Q3: The Third quartile of datas (%75)). Normality distribution was checked with Shapiro-Wilk Test. Mann Whitney U Test was used to compare the means of quantitative variables between groups. A p-value <0.05 was considered significant.

RESULTS

A total of 59 patients were included in the study. Median age, PSA levels, prostate volumes, neutrophil and lymphocyte counts of the patients were 69.0 (63.0-72.0) years, 7.24 (5.50-8.90) ng/dL, 65.0 (60.0-65.0) cc, 6.40 (4.87-8.73) K/uL, and 2.50 (1.60-3.10) K/uL, respectively. While Gleason score upgrading was observed in 18 (30.5%) patients, 11 (18.6%) patients had disease upstaging. Age distribution and prostate volumes were similar in patients in groups 1 and 2 (p=0.424 and p=0.176, respectively). In addition, PSA levels of cases in Group 1 were 8.06 (7.6-9.01) ng/dL, which was significantly higher than those in Group 2 (p=0.012). However, NLR was 1.94 (1.68-3.76) and 3.54 (1.89-5.45) in Group 2 and Group 1, respectively. Although these values were higher in Group 1, the difference was not statistically significant (p=0.266) (Table 1). Similarly, there was no difference between the cases in Group 3 and Group 4 in terms of age and prostate volume (p= 0.899 and p= 0.728, respectively). The PSA levels were 6.75 (5.23-8.34) ng/dL in Group 4 and that was significantly lower than those in Group 3 (p=0.049). NLR was calculated as 2.46 (1.52-5.45) in Group 3, while this rate was 2.24 (1.68-4.35) in Group 4. However, it was not statistically significant, albeit higher in Group 3 (p=0.953) (Table 2). A total evaluation of our data revealed no statistically significant difference in other parameters such as NLR, prostate volume, and age in patients with upstaging and upgrading, except for PSA .

Table 1. Distribution of quantitative values in terms of upgrading

	Upgrading		p
	Group 1 (n:18)	Group 2 (n:41)	
Age(years)	68 (59-72)	70 (63-72)	0.424
PSA (ng/dL)	8.06 (7.6-9.01)	6.2 (5-8.3)	**0.012***
Neutrophil (K/uL)	7.96 (7-10.39)	5.6 (4.27-8.42)	**0.008***
Lymphocyte (K/uL)	2.19 (1.56-3.3)	2.5 (1.63-2.96)	0.773
Neutrophil/Lymphocyte	3.54 (1.89-5.45)	1.94 (1.68-3.76)	0.266
Prostate Volume (cc)	60 (50-65)	65 (60-70)	0.176

Group 1 represents cases with upgrading
Group 2 represents cases without upgrading
The data in the Table are presented as Median (Q1-Q3)
Q1: The first quartile of datas (%25)
Q3: The Third quartile of datas (%75)
Test: Mann Whitney U Test
*p value was considered significant at the 0.05 level

Table 2. Distribution of quantitative data in terms of upstaging

	Upgrading		p
	Group 3 (n:11)	Group 4 (n:48)	
Age (years)	68 (52-75)	69.5 (63-72)	0.899
PSA (ng/dL)	8.06 (8-9)	6.75 (5.23-8.34)	**0.049***
Neutrophil (K/uL)	7.5 (7.45-10.39)	5.68 (4.275-8.53)	**0.044***
Lymphocyte (K/uL)	2.7 (2-4.23)	2.5 (1.58-3.085)	0.413
Neutrophil/Lymphocyte	2.46 (1.52-5.45)	2.24 (1.68-4.35)	0.953
Prostate Volume (cc)	65 (60-65)	65 (57.5-67.5)	0.728

Group 3 represents cases with upstaging
Group 4 represents cases without upstaging
The data in the Table are presented as Median (Q1-Q3)
Q1: The first quartile of datas (%25)
Q3: The Third quartile of datas (%75)
Test: Mann Whitney U Test
*p value was considered significant at the 0.05 level

DISCUSSION

Today, PSA screening can routinely be practiced in almost any health institution. As a result, a significant increase is observed in the number of cases diagnosed with low-risk prostate cancer. In this context, broad-based epidemiological studies show that deaths due to prostate cancer have decreased by one third. However, it is observed that clinicians struggle more intensely with complications observed after curative treatment options such as radical prostatectomy or radiotherapy in cases with low-risk prostate cancer, due to the increasing number of cases (4). Today, radical prostatectomy can be performed with open, retropubic, perineal, laparoscopic, or robot-assisted surgery. Numerous complications may be encountered after radical prostatectomy such as lymphocele, wound infection, deep vein thrombosis, pulmonary embolism, erectile dysfunction, incontinence, and bladder neck contracture. Previous studies report that complications are observed in a wide range, ranging from 5% to 26%, depending on the clinician's experience in surgical techniques and their clinics (10). Another treatment strategy in low-risk prostate cancer cases is radiotherapy. Many gastrointestinal, genitourinary, and psychosocial side effects can be observed in the early or late period after radiotherapy, although it varies in connection with the medical condition of the patients (diabetes mellitus, chronic intestinal diseases, abdominal surgery history), the dose, and technique applied. Some studies reported the interruption of treatment due to acute side effects, up to 10% in the previous periods (11). Active surveillance is another approach for patients with low-risk prostate cancer. This approach has gained great importance in protecting the patient from complications that may arise in curative treatment. Because broad-based epidemiological studies show that cancer-related 10-year mortality rates are lower than 1% in patients with low-risk prostate cancer (12). The studies of Wilt et al. which included 731 localized prostate cancer cases with at least 12 years of follow-up reported no difference in mortality rates of radical prostatectomy and observational follow-up (13). In the United States, active surveillance rates, which were 6.2% for low-risk prostate cancers earlier this century, are reported to have risen to 40% in the past decade (14). Although suitability criteria for active surveillance differ slightly from center to center, many authors suggest that the ideal group consists of cases in T1c and T2a stages, with a Gleason score of ≤6, PSA <10 ng/mL, and involvement of ≤50% in positive cores (8).

Prostate cancer shows a heterogeneous character in terms of biochemical, genetic and histopathological features. Relatedly, recent studies show that radical prostatectomy results are not compatible with the preoperative period when performed in some low-risk patients suitable for active surveillance. A study by Hwang et al. where they examined 1159 radical prostatectomy results found postoperative upstaging in 47.5% of patients with low-risk prostate cancer (9). In another study, Sooriakumaran et al. discussed the outcomes of 750 patients who underwent radical prostatectomy and observed either disease upgrading or upstaging in 40.4% of the patients in the postoperative analysis of surgical specimens (15). Similarly, Conti et al. examined the patients who are suitable for active surveillance criteria in detail after radical prostatectomy and reported upgrading in 23-35% of them, extracapsular invasion in 7-19%, and seminal vesicle involvement in 2-9% (16). In this context, many additional molecules such as prostate cancer antigen 3, sarcosine, and human kallikrein-related peptidase 2 have currently been studied to evaluate the suitability of active surveillance in patient groups (5, 17). However, these markers are very difficult to work and repeat and they put a heavy burden on the health economy. This has led researchers to focus on other easy-to-use diagnostic tools. One of these approaches is NLR, which is based on the relationship between inflammation and cancer.

Inflammation is a natural reaction of metabolism to environmental stimuli, and its main role is the regulation of tissue physiology. Continuation of these processes

for a long time may cause chronic inflammation which may lead to a large number of pathologies, especially cancer (18). Although the relationship between inflammation and cancer has been focused on recently, it was Rudolf Virchow who showed the presence of leukocytes around the tumor for the first time. Tumor, stromal, and inflammatory cells surrounding these cells interact coordinately to form an inflammatory tumor microenvironment. The tumor microenvironment is a highly interactive, organized, and dynamic environment. T lymphocytes, natural killer cells, and tumor-associated macrophages are the major inflammatory cells involved in the tumor microenvironment (19). Various cytokines such as IL1, IL6, TNF-α, and transcription factors such as AP1, NF-kB, STAT3 have a critical role in both inflammation and tumor development in direct connection with the tumor microenvironment (20). Infectious diseases and chronic inflammation are predicted to constitute approximately one-fourth of the causes of cancer (21). Barret esophagitis and esophageal cancer, inflammatory bowel diseases and colon cancer, Schistosoma haematobium and bladder cancer, helicobacter and stomach cancer, and Ebstain Barr virus and nasopharyngeal cancer are the best examples of this condition (18,22). Besides, chemical carcinogens such as tobacco use and exposure to asbestos play a role in cancer etiology by causing several inflammatory reactions, as revealed by many studies (23). In direct connection with this, many analysis report positive effects of both the reduction of chemical exposure or infective factors and the use of anti-inflammatory molecules on cancer development (24). Inflammation in the prostate gland causes major changes in the microenvironment of epithelial cells. These changes result in tissue migration of macrophages, mast cells, and lymphocytes as well as fibroblast activation and stromal remodeling. A large number of cytokines, oxidative stress, and proliferation of epithelial cells that occur after immune response constitute genomic instability, which is directly associated with malignant transformation (7,25). Previous studies investigated this relationship between cancer and inflammation in patients with prostate cancer in detail. In their studies evaluating the results of 173 radical prostatectomies, Ergin et al. brought the result to the literature that higher NLR levels were significantly associated with high-grade prostate cancer (26). Langsenlehner et al. evaluated 415 radiotherapy-treated patients with prostate cancer and reported that NLR is an independent prognostic marker (27). A different study by Lee et al. evaluated 1367 patients with localized prostate cancer who underwent radical prostatectomy operation and reported that NLR was associated with clinicopathological outcomes and worse biochemical recurrence (28). On the other hand, İpekçi et al. did not establish a relationship between NLR and PSA, surgical stage, Gleason score, surgical margin positivity, and third-month biochemical recurrence in their studies evaluating 140 patients who underwent radical prostatectomy for localized prostate cancer (29). In a similar study Gokce et al. evaluated 210 ith low-risk prostate cancer patients eligible for active surveillance (5). After their analysis, they concluded that NLR is a predictor of Gleason upgrading and biochemical recurrence, but not disease upstaging in patients with low-risk prostate cancer. However Zanaty et al. could not establish a relationship between NLR and biochemical recurrence in prostate cancer patients (30). Our study evaluated prostate cancer cases who underwent radical prostatectomy, although active surveillance was among the treatment options. NLR was statistically insignificantly high in patients with upstaging and upgrading in pathology specimens. The results we obtained have led us to conclude that NLR alone does not have clinical significance in low-risk prostate cancer cases.

LIMITATIONS

The main limitations of our study are that our data analysis was performed retrospectively, the number of patients was very limited and short and long-term follow-up results such as biochemical recruitment, disease-free survival, and postoperative surgical complications were not presented.

CONCLUSION

The data from our study have led us to conclude that NLR alone was not an adequate marker in predicting both disease upgrading and upstanding after radical prostatectomy in patients with low-grade prostate cancer suitable for active surveillance. We think that our results should be analyzed in multi-center, prospective, and large series studies to answer the question of which prostate cancer patient is more suitable for active surveillance.

Competing interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical approval: Tokat Gaziosmanpasa University, Ethics Committee, Confirmation number: 20-KAEK-211.

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