

# Is there a correlation between the aggressiveness of chronic asymptomatic prostatitis National Institutes of Health category IV and the Gleason score in patients with prostate cancer?

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## Abstract

**Introduction:** We evaluated the correlation between the International Society of Urological Pathology (ISUP) grades and the aggressiveness grades of prostate inflammation in newly diagnosed prostate cancer patients with chronic asymptomatic prostatitis National Institutes of Health (NIH) category IV (CAPNIHIV).

**Methods:** The study comprised 357 consecutive patients with prostate cancer in whom a cancer diagnosis had been made via a prostate needle biopsy. Histological sections of the prostate biopsy specimens of the patients were reviewed and scored. Prostatic inflammation was scored using the aggressiveness grade of inflammation. The associations between the ISUP grades and the aggressiveness grades of inflammation were analyzed using logistic regression. The limitations of the study were its retrospective design and the limited number of cases.

**Results:** In 110 (31%) patients, CAPNIHIV was detected: 56 (51%) patients had a grade 0 aggressiveness score, 34 (31%) patients had a grade 1 aggressiveness score, and 20 (18%) patients had a grade 2 aggressiveness score. The patients who had prostatic inflammation had 1.65 times (95% confidence interval [CI] 1.05–2.61) greater likelihood of a high ISUP grade (grade  $\geq 3$ ) compared with the patients who did not have prostatic inflammation. The association between the ISUP grade and the aggressiveness grade of inflammation was more pronounced for a grade 2 aggressiveness score ( $n=20$ ; odds ratio 2.97; 95% CI 1.14–7.71).

**Conclusions:** In prostate cancer patients with CAPNIHIV, there was a positive correlation between the inflammation aggressiveness grade and the ISUP grade. The aggressiveness of intraprostatic inflammation may be an important morphological factor affecting the Gleason score.

## Introduction

Prostate cancer is one of the most common types of cancer diagnosed by urologists, and the prostate biopsy is the standard diagnostic method for prostate cancer.<sup>1</sup> Prostatic inflammation is one of the most frequent findings on histopathological examination of prostate biopsy specimens.<sup>2,3</sup> According to the classification of the National Institutes of Health (NIH), asymptomatic inflammatory prostatitis, or NIH category IV prostatitis, is described as the presence of inflammatory cells in the histopathological examination of prostate specimens or in expressed prostatic secretions.<sup>2,4</sup>

In some studies, a positive relationship has been reported between chronic prostate inflammation and prostate cancer risk.<sup>5-8</sup> In case-controlled trials, the presence of the *Trichomonas vaginalis* antibody was found to be positively associated with the incidence of prostate cancer.<sup>9</sup> Similarly, it has been reported that sexually transmitted infections, such as syphilis and gonorrhea, increase the risk of prostate cancer.<sup>10</sup> It can be deduced that these infectious agents may increase the risk of prostate cancer by leading to chronic inflammation in the prostate.<sup>11</sup>

Gleason scoring is the most common method for the histopathological evaluation of prostate cancer.<sup>12</sup> Furthermore, the Gleason score is one of the most important prognostic factors used in predicting the prognosis and choice of treatment for prostate cancer.<sup>13</sup> A new Gleason grading system consisting of five grades was defined for prostatic carcinoma at the 2014 International Society of Urological Pathology (ISUP) Consensus Conference: grade 1 (Gleason score  $\leq 3+3$ ), grade 2 (Gleason score 3+4), grade 3 (Gleason score 4+3), grade 4 (Gleason score 3+5, 5+3, 4+4), and grade 5 (Gleason score 9–10).<sup>14,15</sup>

In this study, we evaluated the association between the ISUP grades and the aggressiveness grades of inflammation in newly diagnosed prostate cancer patients with asymptomatic inflammatory prostatitis.

## Methods

The study protocol was reviewed and approved by the Institutional Review Board of Turkiye Yuksek Ihtisas Training and Research Hospital (Date:12.11.2013, approval No: 311).

### Patients and study design

In this retrospective study, the data of patients from whom 12 core biopsies were taken over a five-year period under the guidance of transrectal ultrasonography were evaluated. The medical history of each patient was obtained before taking the prostate biopsies, which were evaluated from clinical and laboratory perspectives in detail. The complete blood count, urine analysis, and serum total prostate-specific antigen (tPSA) level of each patient was measured. Digital rectal examination (DRE) and uroflowmetry were performed, and an International Prostate Symptom Score (IPSS) was calculated. Under the guidance of transrectal ultrasonography, the patients with abnormal DRE findings and/or prostate cancer suspicion because of high serum tPSA levels ( $\geq 4$  ng/ml) underwent prostate biopsies. The prostate volumes of the patients were calculated using transrectal ultrasonography.

There were 364 patients whose histopathological examinations showed prostate cancer. The study exclusion criteria were a history of clinical prostatitis before the prostate biopsy, a catheterization history due to urinary retention, and a re-biopsy due to an atypical small acinar proliferation or high-grade prostatic intraepithelial neoplasia. Of these 364 patients, seven were excluded: two patients who had had a history of prostatitis before the prostate biopsy and three patients to whom catheterization had been applied due to acute urinary retention were not included in the study. In addition, two patients who had undergone re-biopsies because atypical small acinar proliferation had been found in their initial biopsies were not included in the study. Accordingly, a total of 357 patients were included in the study.

The ISUP grades of the patients included in our study were determined. In their study, Gurel et al classified cases as low-grade (Gleason sum  $< 7$ ) and high-grade (Gleason sum 7–10), while Platz et al classified cases as ISUP grades 1–2 and ISUP grades 3–5.<sup>5,16</sup> Similarly, in our study, the patients with ISUP grades 1–2 were classified as having a low ISUP grade, and the patients with ISUP grades 3–5 were classified as having a high ISUP grade.

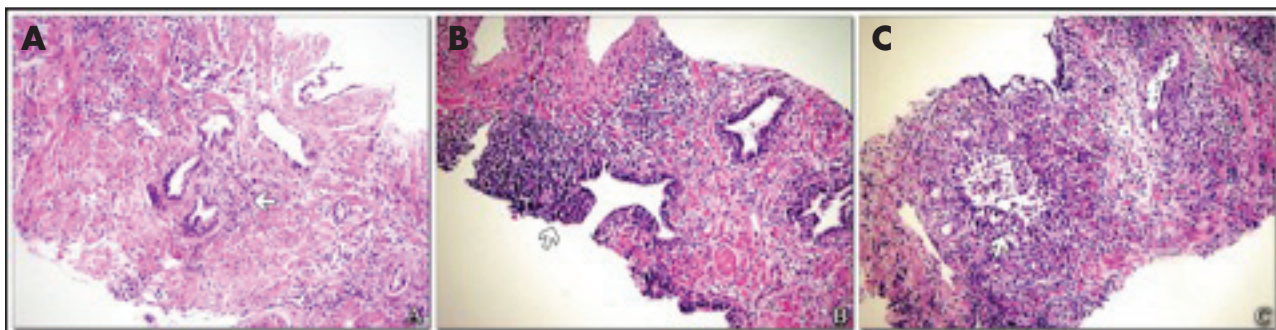
The age, ISUP grade, tPSA value, and prostate volume of each patient were recorded. Hematoxylin–eosin-stained histological sections of the prostate biopsy specimens of the 357 patients were reviewed and scored by two experienced pathologists. The pathologists performing the evaluation were not informed about the purpose of the study. Prostatic inflammation was scored for the aggressiveness grade of inflammation using the grading system reported by Irani et al: grade 0=no contact between glandular epithelium and inflammatory cells infiltrate (intact epithelial cells); grade 1=contact between glandular epithelium and inflammatory cells infiltrate (without glandular epithelium disruption); grade 2=interstitial inflammatory cells infiltrate associated with a clear, less than 25% glandular epithelium disruption in the examined material; and grade 3=more than 25% glandular epithelium disruption in the examined material (Fig. 1).<sup>2,17</sup>

Among the patients, 110 had prostate cancer together with asymptomatic inflammatory prostatitis, and they were classified as grade 0, grade 1, and grade 2 according to their aggressiveness scores of inflammation.

The mean age, prostate volume, and tPSA values of the patients with and without prostatic inflammation were compared. The association between the ISUP grade and the aggressiveness grade of inflammation was evaluated.

### Statistical analysis

A statistical analysis was performed using SPSS® software. Comparisons between the ages, prostatic volumes, and



**Fig. 1.** Scoring for aggressiveness grade of chronic inflammation in prostate needle biopsy. Hematoxylin-Eosin, x200. **(A)** Grade 0=There isn't contact between glandular epithelium and inflammatory cells infiltrate (intact epithelial cells). **(B)** Grade 1=There is contact between glandular epithelium and inflammatory cells infiltrate (without glandular epithelium disruption). **(C)** Grade 2=Interstitial inflammatory cells infiltrate associated with a clear, less than 25% glandular epithelium disruption in the examined material.

serum tPSA levels of the patients were performed by t-tests and one-way ANOVA tests (value of significance  $p < 0.05$ ). The correlation between the tPSA and the aggressiveness grade of inflammation was determined by Pearson correlation analysis (value of significance  $p < 0.05$ ). The odds ratios (ORs) and 95% confidence intervals (CIs) for the associations between the ISUP grades and the aggressiveness grades of prostatic inflammation were calculated using logistic regression analysis.

## Results

### Patient characteristics

The characteristics of the 357 patients who were included in the study are presented in Table 1. In the histopathological examination, 247 (69%) patients with prostate cancer had no asymptomatic inflammatory prostatitis, while 110 (31%) patients with prostate cancer had asymptomatic inflammatory prostatitis. The aggressiveness grade distribution of the 110 patients with chronic prostatic inflammation was as follows: 56 (51%) patients were grade 0, 34 (31%) patients were grade 1, and 20 (18%) patients were grade 2. There were no patients with an aggressiveness score of grade 3. In one patient, there was no clear distinction between the aggressiveness scores of grades 2 and 3, so this patient was included in the patient group with aggressiveness scores of grade 2.

There was no statistically significant difference in terms of age and prostate volume between the patients with and without asymptomatic inflammatory prostatitis. However, the tPSA values were significantly higher in the patients with prostate inflammation. When the group of patients without asymptomatic inflammatory prostatitis and the group of patients with inflammation aggressiveness scores of grades 0 and 1 were compared, no significant difference was observed between the tPSA values. In contrast, the tPSA values of the patient group with grade 2 inflammation aggressiveness were found to be significantly higher than those of all the other groups. There was no significant difference between mean

tPSA values of aggressiveness grade 0 and aggressiveness grade 1 patients (Table 1). There was a positive correlation between tPSA and the aggressiveness grade of inflammation ( $r=0.234$ ,  $p \leq 0.001$ , Pearson correlation).

Table 2 presents the distribution of patients according to ISUP grade. Of the 357 patients, 151 (42%) patients had high ISUP grades and 206 (58%) patients had low ISUP grades. Of the 247 patients without asymptomatic inflammatory prostatitis, 95 (38%) patients had high ISUP grades and 152 (62%) patients had low ISUP grades. Of the 110 patients with asymptomatic inflammatory prostatitis, 56 (51%) patients had high ISUP grades and 54 (49%) patients had low ISUP grades (Table 2).

### Association of aggressiveness of inflammation with ISUP grade

Table 3 provides the ORs of the high ISUP grade in relation to the aggressiveness grade of inflammation. Patients with prostatic inflammation had nearly a 65% higher likelihood of a high ISUP grade (OR 1.65, 95% CI 1.05–2.61) than the patients who did not have prostatic inflammation. In patients with a grade 2 aggressiveness score, this association was significantly more prominent (OR 2.97, 95% CI 1.14–7.71). When compared to the patients without prostatic inflammation, the likelihood of a high ISUP grade increased from a grade 0 aggressiveness score (OR 1.29, 95% CI 0.71–2.31) to a grade 2 aggressiveness score (OR 2.97, 95% CI 1.14–7.71;  $p=0.02$ ) in the patients with prostatic inflammation. As the aggressivity of inflammation increased, the probability of a high ISUP grade also increased (Table 3, Fig. 2).

## Discussion

The results of our study showed that the probability of a high ISUP grade was higher in prostate cancer patients with asymptomatic inflammatory prostatitis diagnosed via a prostate needle biopsy. As the aggressiveness grade of inflammation increased, the likelihood of a high ISUP grade also increased. This relationship was considerably more prominent in the patients with a grade 2 aggressiveness score.

**Table 1. Characteristics of prostate cancer cases and prostate cancer together with asymptomatic inflammatory prostatitis cases**

	Total	PCa	PCa + chronic inflammation			
			Total	Aggressiveness of inflammation		
				Grade 0	Grade 1	Grade 2
n (%)	357	247 (69)	110 (31)	56 (51)	34 (31)	20 (18)
Mean age	67.7	67.3	68.6	68.7	68.8	67.9
Mean prostate volume (ml)	56.7	55.8	58.9	57.2	58.0	65.3
Mean PSA(ng/mL)	9.0	8.2 <sup>b</sup>	10.8 <sup>a</sup>	8.7 <sup>c</sup>	10.6 <sup>d</sup>	16.7

<sup>a</sup> $p=0.003$  (p value from a t-test), compared with PCa group. <sup>b-d</sup> $p < 0.0001$ ,  $p < 0.0001$ ,  $p < 0.05$ , respectively (p value from a one-way ANOVA test), compared with aggressiveness grade 2 group.

PCa: prostate cancer without asymptomatic inflammatory prostatitis; PCa + chronic inflammation: prostate cancer together with asymptomatic inflammatory prostatitis; PSA: prostate-specific antigen.



**Table 2. Distribution of patients according to ISUP grade**

	Total	PCa	PCa + chronic inflammation
N (%)	357	247(69%)	110 (31%)
ISUP grade			
High (ISUP 3–5), n (%)	151 (42%)	95 (38%)	56 (51%)
Low (ISUP 1–2), n (%)	206 (58%)	152 (62%)	54 (49%)

ISUP: International Society of Urological Pathology; PCa: prostate cancer without asymptomatic inflammatory prostatitis; PCa + chronic inflammation: prostate cancer together with asymptomatic inflammatory prostatitis.

These results support the hypothesis that asymptomatic inflammatory prostatitis affects the development of prostate cancer with a high ISUP grade.

As in many cancer types, the course of prostate cancer is different for each patient. In patients with prostate cancer, various prognostic factors and nomograms are used to predict the course the disease will follow. The Gleason grading system used in prostate cancer is one of the most important prognostic factors and has been shown to be a good indicator of survival.<sup>12,13</sup>

Prostatic inflammation is one of the most common findings in the histopathological examination of prostate biopsy specimens.<sup>2,3</sup> In prostate biopsies, asymptomatic inflammatory prostatitis has been reported at a rate of 32–44%.<sup>1,18,19</sup> In our study, asymptomatic inflammatory prostatitis was detected in 31% of 357 patients — compatible with the rates reported in the literature.

Symptomatic prostatitis significantly increases serum tPSA levels.<sup>20</sup> Notwithstanding, in some studies, asymptomatic inflammatory prostatitis was found not to significantly affect serum tPSA levels.<sup>21</sup> However, the common view is that asymptomatic inflammatory prostatitis may significantly increase serum tPSA levels.<sup>2,4,22</sup> Serum tPSA levels have also been found to be higher in patients with excess intraprostatic inflammation.<sup>4,23</sup> Yaman et al reported that there is a significant correlation between the aggressiveness grade of subclinical prostatic inflammation and PSA.<sup>23</sup> In the present study, there was also a positive correlation between the aggressiveness of chronic inflammation and PSA: the serum tPSA levels were found to be significantly higher in the patients with prostate cancer whose aggressiveness grade was 2.

While some studies have reported that there is no positive relationship between chronic inflammation and prostate cancer,<sup>24,25</sup> many have found a positive correlation between chronic prostate inflammation and prostate cancer risk.<sup>5-8,11,16</sup> In a study on the impact of chronic inflammation on prostate cancer progression, it was found that chronic inflammation can increase the possibility of prostate cancer. In the study, Gurel et al found that intraprostatic inflammation is associated with a high-grade prostate cancer etiology.<sup>16</sup> Supporting their hypothesis, the ISUP grade was found to be high in the patients with an elevated chronic inflammation aggressivity

**Table 3. In prostate cancer patients together with asymptomatic inflammatory prostatitis, the odds ratio values for high ISUP grade according to the aggressiveness grade of inflammation**

	n	High ISUP grade (ISUP 3–5)	OR	95% CI
Prostatic inflammation, No	247	1.00	Reference	
Prostatic inflammation, Yes <sup>a,b</sup>	110	1.65	1.05–2.61	
Aggressiveness grade of inflammation				
Grade 0	56	1.29	0.71–2.31	
Grade 1	34	1.80	0.87–3.70	
Grade 2 <sup>b</sup>	20	2.97	1.14–7.71	

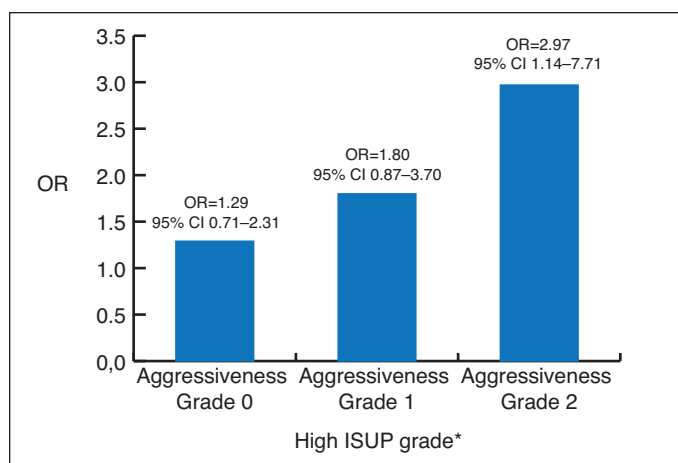
<sup>a</sup>All patients with any aggressiveness grade of inflammation. <sup>b</sup>p=0.02. CI: confidence interval; ISUP: International Society of Urological Pathology; OR: odds ratio.

grade in our study as well. The results reported in the literature and in our work are different from those of the REDUCE trial. In the REDUCE trial, the patients with inflammation but no prostate cancer as determined by a needle biopsy had a lower likelihood of developing prostate cancer in the future.<sup>26</sup> However, the PSA concentrations of the men included in the study ranged from 2.5–10 ng/mL. In our study, all prostate cancer patients were included, regardless of their serum tPSA levels.

In a study by Irani et al, both inflammatory infiltration and aggressiveness of prostatic inflammation were graded for asymptomatic inflammatory prostatitis. Inflammatory infiltration grading has four scores: grade 0: no inflammatory cells; grade 1: inflammatory cells scattered into the stroma without lymphoid nodules; grade 2: separate (non-associated) lymphoid nodules; and grade 3: combination of infiltrate forming large areas of inflammation.<sup>17</sup> As we aimed to investigate the correlation between the Gleason score and aggressiveness of asymptomatic inflammatory prostatitis in this study, only the aggressiveness score of prostatic inflammation was included; not performing the grading of inflammatory infiltration can be considered one of the limitations of our study.

In patients with asymptomatic inflammatory prostatitis, the incidence of grade 3 aggressiveness score has been reported to be low. In a study of Irani et al in which grading the aggressiveness of prostatic inflammation was performed, only two (1.8%) of 111 patients with asymptomatic inflammatory prostatitis were reported to have grade 3 aggressiveness score.<sup>17</sup> In our study, 110 patients had asymptomatic inflammatory prostatitis, but histopathological examination by experienced pathologists did not report a case of grade 3 aggressiveness score. This may be due to the low incidence of grade 3 aggressiveness score.

In some studies, intraprostatic inflammation has been found to be a prognostic factor for prostate cancer. Another study by Irani et al determined that the biochemical recur-



**Fig 2.** Associations between the aggressiveness grade of inflammation and the high International Society of Urological Pathology (ISUP) grade (ISUP grade 3–5). As the aggressiveness of inflammation increased, the odds of the high ISUP grade (ISUP grade 3–5) was also increased. \*Based on literature studies, cases were classified as low ISUP grade and high ISUP grade.<sup>5,16</sup> CI: confidence interval; OR: odds ratio.

rence rate was significantly high in patients with high-grade inflammation after radical prostatectomy. Authors hypothesized that chronic inflammation is an independent prognostic factor for disease-free survival in patients who underwent radical prostatectomy due to localized prostate cancer.<sup>27</sup> Meanwhile, Davidsson et al investigated the prognostic significance of morphological changes in prostate tissue during prostate cancer and showed that moderate or severe chronic inflammation may have prognostic significance for prostate cancer.<sup>28</sup> The significant association between high aggressiveness-scored inflammation and high ISUP grade in our study supports these hypotheses.

The effect of the existence of asymptomatic inflammatory prostatitis on the course of prostate cancer has not been confirmed, and further research is required. The present study found support for the relationship between prostatic inflammation and prostate cancer. The limitations of the study were that it was conducted retrospectively, the number of patients was small, and the results were not compared with the Gleason score in radical prostatectomy specimens. A further limitation is the lack of infiltration grading of inflammation. A prospective study using a larger patient sample is warranted.

## Conclusions

This study determined that in newly diagnosed prostate cancer patients with asymptomatic inflammatory prostatitis, the likelihood of a high ISUP grade increased as the grade of aggressiveness of inflammation increased. The aggressiveness of intraprostatic inflammation may be an important morphological factor affecting Gleason scores. Whether or not intraprostatic chronic inflammation is a prognostic criterion in prostate cancer should be considered a future research topic.

**Competing interests:** The authors report no competing personal or financial interests related to this work.

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