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Original Article

Comparison of the ESR and CRP levels and their relationship with PSA in benign prostate hyperplasia and prostate adenocarcinoma patients: A retrospective analytical study

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Abstract. Prostate cancer is the most common malignancy (excluding skin malignancies) in men. Chronic inflammation has been shown to be associated with cancer. Although this association has not been proven for prostate cancer, evidence shows that inflammation has a possible role in prostate cancer. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are the two key indices in assessing inflammation. It was therefore decided to investigate ESR and CRP in patients with prostate cancer and assess their relationship with PSA level at initial diagnosis. In this retrospective-analytical study, hospital records of all patients referred to Mortaz and Shahid Rahnemoon general hospitals during 2013-2018 and undergoing prostatectomy with pathology reports of benign prostatic hyperplasia or prostate adenocarcinoma were extracted by census method. The required variables including patient's age, PSA, ESR and CRP levels were extracted from hospital records. Extracted data were analyzed by ANOVA and Chi-square tests in SPSS software version 18. P-value <0.05 was considered statistically significant. According to the results, patients' mean age was 70.71±10.19 years, mean ESR 38.86±31.28, and mean CRP 1.28±1.01. There was a significant difference between the two groups in mean values of ESR and CRP (P<0.05). The results also showed meaningful correlations between age and PSA, ESR and PSA, CRP and PSA, and CRP and ESR in patients with prostate cancer (P<0.05). As inflammatory factors, ESR and CRP increase in patients with prostate cancer, they can be used in the initial diagnosis of prostate cancer as an adjunct diagnostic assay and prognostic factor (only ESR) in conjunction with PSA.

Keywords: Neoplasm, prostate, blood sedimentation, inflammation

Introduction

Prostate cancer is the most common malignancy (other than skin) in men in the United States of America (USA), and the second leading cause of cancer-related death in the western world [1]. There are no accurate statistics on the prevalence of prostate cancer in Iran, but investigations suggest that its prevalence is lower in Iran compared to western countries and USA [1, 2]. Although available information for treatment of prostate cancer has increased [3-5], prognosis for advanced stage patients is unfortunately associated with mean survival of 2.5 years [6]. Long-term chronic inflammation is associated with infectious cancers such as stomach, liver, and colon cancers, which are commonly seen in patients with intestinal inflammation [7]. It is thought that chronic inflammation stimulates cancer through a variety of mechanisms, including irreversible cell and DNA damage by producing free radicals, and accelerated cell development through DNA and cell transcription [8].

Although the role of chronic inflammation or return of inflammation in the progress of prostate cancer has not been proven, a number of reports suggest the possible role of inflammation in prostate cancer through various interrelated mechanisms [9]. Inflammation may be associated with prostate carcinogenesis and is often seen in prostate biopsy, radical prostatectomy samples and tissues taken to treat BPH. In histological terms, inflammatory cells are commonly found in and around the center of atrophy and identified by increased proliferation index. This center that is also known as proliferative inflammatory atrophy, maybe the initial indicator of prostate cancer or an indicator of an appropriate environment for development of prostate cancer [7].

Serum inflammatory markers had significantly elevated

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TABLE 1
MEAN VARIABLES BY GROUPS (PROSTATE ADENOCARCINOMA (PAD) & BENIGN PROSTATIC HYPERPLASIA (BPH)

Variable	Mean ± SD			P-value*
	PAD (n=145)	BPH (n=145)	Total (n=290)	
Age	70.71±10.19	69.97±11.18	71.44±9.07	0.22
ESR	38.86±31.26	19.39±7.51	58.32±33.84	0.001
CRP	1.28±1.01	0.57±0.49	1.99±0.9	0.001

TABLE 2
MEAN PSA BY AGE GROUP IN PATIENTS WITH PROSTATE CANCER

Variable	Age range (yrs)				P-value*
	34-64 (n=44)	65-74 (n=40)	75-102 (n=61)	Total (n=145)	
PSA	43±18.94	40.98±23.21	53.31±25.14	46.78±23.41	0.014

TABLE 3
MEAN PSA IN DIFFERENT AGE GROUPS OF PATIENTS WITH PROSTATE CANCER

Age group	P-value*		
	34-64	65-74	75-102
34-64	-	0.686	0.024
65-74	0.686	-	0.009
75-102	0.024	0.009	-

*LSD test

in patients with prostate cancer, especially in those with higher Gleason and PSA scores [10]. Measurement of Erythrocyte Sedimentation Rate (ESR) is a simple and inexpensive laboratory test, and is used in assessing the acute phase [11]. ESR has prognostic value in several cancers, including prostate cancer [12-18]. ESR is an indicator of increased risk and death in prostate cancer, and is likely to reflect the relationship between tumor and the host [19]. ESR has been shown to predict survival rate in early stages of localized prostate cancer [20]. C-reactive protein (CRP) is a general inflammation marker, and is associated with prostate cancer. Increased CRP indicates poor prognosis [21, 22], and is high in men with bone metastasis [23]. There is also a strong relationship between CRP and PSA, irrespective of the stage of the tumor, which suggests that inflammation may be the basis of prostate cancer [24, 25]. Measurement of plasma CRP level does not support diagnosis of benign conditions in patients with increased PSA levels, even though plasma CRP levels have a good correlation with plasma PSA levels in patients with prostate cancer, and suggest a strong relationship between inflammation and prostate cancer [26].

The present study investigates ESR and CRP levels in patients with prostate cancer and their relationship with PSA in initial diagnosis, and the results will be used for better treatment and management of prostate cancer.

Materials and Methods

Study design

In this retrospective- analytical study, hospital records of all patients referred to Mortaz and Shahid Rahnemoon general hospitals during 2013-2018 and undergoing prostatectomy with pathology reports of benign prostatic hyperplasia or prostate adenocarcinoma were extracted by census method. The required variables including patient's age, PSA, ESR and CRP levels were extracted from hospital records. Extracted data were analyzed by ANOVA and Chi -square tests in SPSS software version 18. P-value <0.05 was considered statistically significant.

Exclusion criteria

Patients with inflammatory diseases (arthritis, vasculitis…), rheumatoid arthritis, gout, asthma, chronic lung diseases, heart attacks or apoplexies, and those using NSAID were excluded.

Data sources/measurement

Patients' demographic details and PSA, ESR, and CRP levels were extracted from their hospital records and inserted in a checklist. Pathology reports of BPH and prostate adenocarcinoma patients were included in the checklist. All glass slides were reassessed by two pathologists for the coordination of grading based on the new Gleason grading of the World Health Organization (2016).

Statistical methods

Data collected were analyzed in SPSS-18 using T- test, LSD, ANOVA, and correlation tests. Logistic regression was used to eliminate the effect of confounding variables and determine the relationship between independent variables and cancer. P value less than 0.05 was considered statistically significant.

Ethical considerations

The study was given ethical approval with Ethical Committee of the Medical school of Shahid Sadoughi University of Medical sciences and Shahid Rahnemoon educational hospital and Mortaz general Hospital and all the patients had given written informed consent as a role in first admission and hospitalization.

Results

A total of 290 patients were enrolled in the study by census method. One hundred forty- five benign prostatic hyperplasia patients and also 145 with prostate adenocarcinoma. According to the results, patients' mean age was 70.71±10.19 years ranging from 34 to 102 year.

Mean values of ESR and CRP were significantly higher in the group with benign prostatic hyperplasia compared to the patients with prostate adenocarcinoma

The results relating to different variables (age, ESR, and CRP) by groups showed mean age of 69.97±11.18 years in benign prostatic hyperplasia (BPH) patients and 71.44±9.07 years in patients with prostate adenocarcinoma (PAD). Other data are presented in Table 1. ANOVA test results showed significant differences between two groups in mean values of ESR (P=0.001) and CRP (P=0.001). In other words, Mean values of ESR and CRP were

TABLE 4
MEAN VALUE OF VARIABLES BY GLEASON SCORE IN PATIENTS WITH PROSTATE CANCER

Variable	Gleason Score				P-value
	Well-differentiated (n=23)	Moderately differentiated (n=24)	Poorly differentiated (n=98)	Total (n=145)	
ESR	42.74±17.81	55.08±18.16	62.77±38.34	58.32±33.84	0.032
CRP	1.3±1.02	1.92±0.77	2.17±0.82	1.99±0.9	0.001
PSA	29.87±15.7	47.46±20.85	50.58±23.92	46.78±23.41	0.001

*ANOVA test

TABLE 5
CORRELATION BETWEEN STUDY VARIABLES IN PATIENTS WITH PROSTATE CANCER

Variable	Statistics	Age	PSA	ESR
PSA	Pearson correlation	0.254	-	0.191
	P-value	0.002		0.021
ESR	Pearson correlation	-0.019	0.191	-
	P-value	0.82	0.021	
CRP	Pearson correlation	-0.115	0.214	0.662
	P-value	0.168	0.01	0

*Logistic regression

significantly higher in the PAD patients compared to the BPH. No significant difference was observed between two groups in terms of mean age.

There were significant differences in mean PSA by age group in patients with prostate cancer

The results relating to mean PSA by three age groups of 34-64, 65-74, and 75-102 years in patients with prostate cancer showed mean PSA of 43±18.94 in 34-64 age group, 40.98±23.21 in 65-74 age group, and 53.31±25.14 in 75-102 age group. Other data are shown in Table 2. ANOVA test results showed significant differences in mean PSA by age group in patients with prostate cancer (P=0.014). Thus, LSD test was used to assess two-by-two relationships between groups. LSD test results showed no significant difference between first and second age groups (P=0.686), but the difference between first and third groups and also between second and third age groups was significant (P=0.024, P=0.009 respectively), as shown in Table 3.

No significant differences in mean values of ESR and CRP by age group in patients with prostate cancer were seen

The results relating to mean values of ESR and CRP by three age groups of 34-64, 65-74, and 75-102 years in patients with prostate cancer showed mean ESR of 61±29.93 in 34-64 age group, 56.68±27.91 in 65-74 age group, and 57.46±39.9 in 75-102 age group. ANOVA test results showed no significant differences in mean values of ESR and CRP by age group in patients with prostate cancer (P=0.82, P=0.168 respectively). In other words, the difference between mean values of ESR and CRP in different age groups was not statistically significant.

Significant differences between the ESR, CRP, PSA in terms Gleason score in patients with prostate cancer were seen

The results relating to the frequency of Gleason grading score in patients with prostate cancer showed that of the 145 patients, 32 (22%) were in grade 8. The results relating to mean values of ESR, CRP, and PSA in terms of Well (1-6), Moderate (7-8), and Poorly differentiated (9-10), Gleason scores in patients with prostate cancer showed mean ESR of 42.74±17.81 in Well differentiated group, 55.08±18.16 in Moderately differentiation group, and 62.77±38.34 in Poorly differentiation group. ANOVA test results showed significant differences between these three variables in terms of Gleason score in patients with prostate cancer (P=0.032, P=0.001, P=0.001 respectively for ESR, CRP, PSA in terms of Gleason score). Thus, LSD test was used to assess two-by-two relationships between groups. LSD test results showed significant differences between Well and Poorly differentiated groups in mean ESR, between Well and Poorly differentiated and Well and Moderately differentiated in mean CRP, and between Well and Poorly and Well and Moderately differentiated in mean PSA (P<0.05), as shown in Table 4.

Positive correlations were found between PSA and age, ESR and PSA, CRP and PSA, and CRP and ESR in patients with prostate cancer

Pearson correlation coefficient test showed a positive correlation between PSA and age with r=0.254 and P=0.002. Also, positive correlations were also found between ESR and PSA, CRP and PSA, and CRP and ESR in patients with prostate cancer (P<0.05). Other data are shown in Table 5.

ESR relationship with prostate cancer became significant

Binary logistic regression was used to determine the effect or relationship of each independent variables of age, ESR and CRP with prostate cancer after eliminating the effect of other variables, which confirmed significance of the model (P<0.05). In other words, cancer prediction power of the model significantly increased with inclusion of these three variables in regression model. Correlation coefficient square was found R2=0.877, which is high and shows that 87.7% of variations in the dependent variable are covered by independent variables included in the model. Cancer diagnosis sensitivity and specificity of the above three variables were 91.7% and 97.9% respectively, with accuracy of 94.8%, which are high. Hence, after elimination of the effects of age and CRP on cancer (not significant), the relationship of ESR with prostate cancer became significant (P=0.001), which means that for every unit increase in ESR, risk of cancer increases by 1.38 times in relation to BPH. The above model showed that risk of cancer was not related to age or CRP (P>0.05). The above results will be exactly confirmed with elimination of age and CRP, and the only difference will be in the increase in specificity of cancer diagnosis to 100% and in accuracy to 95.9% Probability of developing cancer was assessed by Log adds using Logistic Regression data, and then ESR with significant relationship was plotted (Figure 1). According to the above Figure, probability of developing prostate cancer with ESR between 0-3 is close to zero. This probability exponentially increases with increasing ESR,

especially when ESR is 30-50. This probability approaches 100% when ESR=50. The graph becomes plateau-like at ESR>50, and further increase in ESR results in no change in probability of cancer.

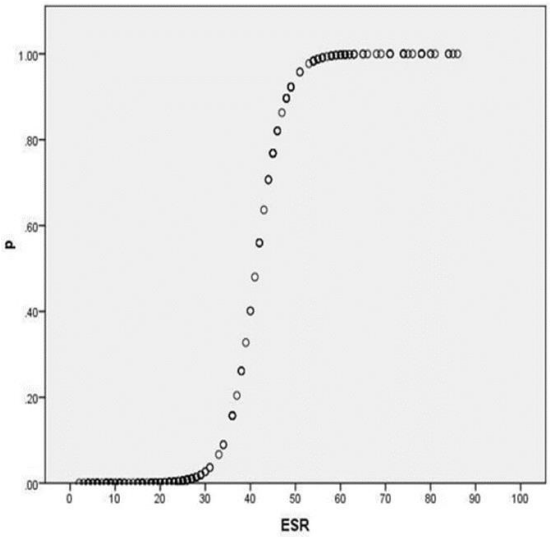

Figure 1 ESR relationship with probability of developing prostate cancer in study subjects

Discussion

The present study aimed to assess ESR and CRP levels in patients with prostate cancer and their relationship with PSA level at initial diagnosis. Significant differences were found between: 1- Mean serum PSA in different age groups of patients with prostate cancer; 2- Mean serum ESR and CRP levels in PAD and BPH patients; and 3- Mean serum ESR, CRP, and PSA and Gleason score (found at Well, Moderate, and Poorly differentiated degrees). No significant difference was found between different age groups of patients with cancer in terms of ESR and CRP levels. The increasing risk of developing prostate cancer was found to have no correlation with age or CRP level. While increasing ESR level is associated with increasing risk of cancer. According to evidence, chronic inflammation is the underlying factor for 20% of all cancers in adults. This inflammation can be induced by infectious or environmental factors. According to previous studies, inflammation has a major role in pathogenesis of prostate cancer, and CRP and ESR are regarded as prognostic inflammatory factors in this cancer [20, 27]. Studies have shown that many cancers (including stomach, liver, and colon cancers) are associated with chronic inflammation [7]. ESR and CRP are two diagnostic tests for inflammation, and are used in diagnosis of acute and chronic inflammation. The role of inflammation in prostate cancer is not fully understood. Although a number of studies have been conducted in this area, and most have used ESR and CRP as diagnostic inflammation tests [9]. The majority of these studies have investigated the prognostic value of ESR and CRP, and some have used ESR and others CRP as prognostic tests in patients with prostate cancer, with high prognostic value. Bing et al. investigated the role of ESR and PSA in prognosis of patients with advanced prostate cancer and reported positive results [28]. In another study, Graff et al. found that increased CRP implies poor prognosis in patients with prostate cancer [29, 30]. The results obtained by Borre et al. showed that ESR is a predictive factor for survival of patients with primary localized prostate cancer (organ limited) [20]. The study by Johansson et al. also referred to the prognostic value of ESR in patients with prostate cancer [19]. The present study results showed that ESR has a high prognostic value, which agrees with some of the above studies [19, 31]. But, no significant relationship showing prognostic value of CRP was found, which disagrees with some of the above studies [32].

In the present study, mean serum PSA was significantly different in different age groups. In a study conducted by Putra et al. on patients with BPH, PSA level was 4.29 in patients younger than 60 years, 4.61 in patients aged 61-69 years, and 4.8 in patients over 70 years of age, which shows that PSA increases with aging. These results can be matched with increasing levels of this marker with aging in the present study, except that Putra et al. study was conducted on patients with BPH [33]. Comparing the results of the present and the above studies suggests that the possible tenfold increase compared to the normal range in PSA levels can help determination of type of neoplasm, but this has to be confirmed in future studies. The present study results showed positive correlations between age and PSA, ESR and PSA, CRP and PSA, and CRP and ESR. Another study conducted by Yun et al. on healthy people attending for check-ups revealed a significant relationship between systemic inflammatory markers such as: ESR and PSA [34].

According to the present study results, ESR and CRP levels are significantly higher in prostate cancer groups compared to BPH group, which is similar to the results obtained in previous studies. In a study conducted by Kim et al. serum CRP level was higher in prostate cancer group compared to BPH group [32]. In agreement with the present study results, Aldemir et al. found that serum inflammatory markers had significantly increased in patients with prostate cancer (especially in those with higher Gleason score and PSA level) [10]. The present study results also showed positive correlations between age and PSA, ESR and CRP, PSA and CRP, and CRP and ESR in patients with prostate cancer. In their study, Chang et al. found a relationship between plasma CRP and serum PSA levels in patients with prostate cancer [26].

Given higher mean values of ESR and CRP in patients with prostate cancer compared to BPH group, and a significant difference between them, it can be concluded that as inflammatory factors, ESR and CRP increase in patients with prostate cancer, and thus they can be used as diagnostic test in diagnosing prostate cancer. Moreover, the positive and significant correlations found between ESR and PSA, CRP and PSA, and CRP and ESR in patients with prostate cancer show that ESR and CRP can have the same diagnostic value as PSA in diagnosing prostate cancer. Considering the significant relationship found between PSA and age groups, PSA can be said to

increase with aging in patients with prostate cancer, and this increase in the over 75-year age group is statistically significant compared to other groups.

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Conflict of Interest

The authors declare that there is no conflict of interest or financial support regarding the publication of this paper.

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