

Association of serum prostate-specific antigen with Complete Blood Counts in patients with prostatic cancer

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Background: Prostate cancer is the second most common cancer and one of the most leading causes of death in men worldwide. The prostate-specific antigen (PSA) as a screening method showed that there has been a slight decrease in prostate cancer mortality. Effective biomarkers in screening and diagnosis would be beneficial for avoiding unnecessary operations. The predictive and prognostic value of complete blood count (CBC) has been manifested by recent studies. We aimed to determine the association of serum PSA with Complete blood counts in patients with prostate cancer.

Method: The present study included 100 subjects, 50 patients diagnosed with new prostate cancer and 50 patients with prostate cancer. All the was undertaken in the central diagnostic laboratory at VIMS and RC. Blood samples were collected from all the subjects after taken permission from the institutional ethics committee and consent form. The haemoglobin, RBCs, MCV, MCHC, RDW will be analysed by using laboratory standard methods (Beckman coulter LH-780) and The serum PSA levels are estimated by commercially available kits based on enzyme-linked immunosorbent assay (ELISA). **Results:** In the present study found significantly elevated levels of a prostate specific antigen in both groups of prostatic cancer patients. The reduced levels of hemoglobin, red blood cells, platelets, neutrophils were observed in prostatic cancer patients when compared to newly diagnosed prostate cancer patients. The PSA levels were negatively correlated with total blood counts. **Conclusion:** This study suggests that the elevated levels of prostate specific antigen were useful for diagnosis and prognosis of prostatic cancers, along with the monitoring of complete blood count may be useful for the treatment of patients with prostatic cancers.

Keywords: Prostate Cancer, PSA, Hemoglobin and RBCs

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Introduction

Prostate cancer (PCa) is also one of the most common cancers in worldwide and diagnostic tools of PC by prostate specific antigen (PSA). The increasing incidence of PCa related mortality rate has been reduced [1-2]. It has been differed in tumor markers and contributes to genetic factors, metabolic disturbances that happen in the prostatic tissue, benign prostatic hyperplasia and prostatic cancer [3-5]. The incidence of prostate cancer varies remarkably in different countries and regions, which increased significantly during the past few decades due to diverse approaches to diagnosing PCa. Despite different treatment methods including radical prostatectomy, hormone deprivation therapy, radiation therapy and chemotherapy were applied, most tumours relapse in 2 years to the castration-resistant state and the prognosis of PCa remains disappointing [6-7]. Given this, it is of interest for clinicians to stratify the high-risk PCa patients who are prone to tumour recurrence and poor prognosis so that clinicians could further identify optimal treatment strategies [8]. The changes in systemic inflammatory response can be reflected by the measurement of various blood-based parameters. A variety of blood-based indexes including C-reactive protein (CRP), modified Glasgow Prognostic Score (mGPS), platelets count and neutrophil-to-lymphocyte ratio (NLR) has been extensively explored to predict the prognosis of cancer patients. A large number of studies have reported that elevation of NLR was associated with poor clinical outcomes in various malignant tumours [9]. In recent years, several studies have reported that an elevation in NLR correlated with biological tumor recurrence and poor prognosis in patients with PCa. The prostate specific antigen and prostate acid phosphatase were used for the diagnosis of prostatic cancer [10]. PSA is a glycoprotein that contains 237 amino acids produced by the lamina of the prostate gland and circulated in the bloodstream exist 2 major forms [11]. The PSA levels are useful for prostate cancer detection and predict prognosis in men with prostate cancer undergoing therapy. The prevalence of symptomatic prostatitis was 9% in men above the age of 40 years, although the prevalence of asymptomatic prostatitis was unknown [12]. In addition, prostatic lesions called proliferative inflammatory atrophy and prostatic intraepithelial neoplasia are considered precursors of prostate cancer [13-14]. This term includes focal atrophic lesions as well as chronic inflammation.

Inflammatory cells release several oxidative materials which may lead to genomic and cellular damage [15]. The predictive and prognostic value of complete blood count (CBC) has been manifested by recent studies. It has been known that there is an association between inflammation and cancer and the use of CBC is the subject of research because of its capability to show an inflammatory process in the early stages of diseases. The results of CBC differ in cancer patients and give us some clues about the prognosis of the disease [16]. This suggests that routine CBC may be used for different purposes such as cancer screening, diagnoses or follow-ups in the future. We aimed to evaluate the serum prostate specific antigen with complete blood counts in patients among two groups of prostatic cancer.

Materials and Methods

Settings: This study was conducted in the Department of Pathology at the Institute of Medical Science, Karnataka.

Duration and Type of The study: This is a cross-sectional observational study conducted from June 2014- Aug 2016.

Sampling Methods: A total of 100 subjects were included in the present study 50 patients diagnosed with Prostate cancer and 50 patients with prostatic cancer on treatment.

Sample Size: 100 Cases

Inclusion Criteria: Patients with prostatic cancer and age more than 30 years were included in the present study.

Exclusion Criteria: Patients with acute indications for surgical intervention such as: refractory hematuria, recurrent UTI, concomitant bladder stones, second renal insufficiency, Urinary Tract Infections, other types of cancers and inguinal hernia were excluded from this study.

Data collection and Procedures: From all subjects, after overnight fasting (12hrs), 6mL of venous blood was collected and 2mL transferred into EDTA tube, remaining 3mL transferred into the plain tube. The collected samples were separated by centrifugation at 4000 rpm for 15 min and stored until biochemical analysis was done. The serum prostate-specific antigen was analysed by using Enzyme-Linked Immunosorbent Assay "ELISA" and the complete blood count were analysed by using standard laboratory methods (Sysmax auto analyzer

Ethical considerations and Permission: All the subjects were recruited in the study after obtaining their informed consent after obtaining of ethical clearance from the institute.

Statistical Analysis: The normal distribution of data was checked by using the Kolmogorov Smirnov test. All the characters are descriptively summarized. The mean and standard deviation of the arithmetic mean were used. Variations in the serum Prostate Specific Antigen (PSA was analysed by using Student’s T-Tests (2 Tailed). The correlation between the PSA, CBC was done by using Pearson Correlation analysis. The Data has been compiled in Microsoft Excel spreadsheets and analyzed using SPSS for windows version 16.0. A p-value <0.05 was considered statistically significant.

Results

Table - 1 shows the mean values and SD of patient’s characteristic’s and various parameters studied in prostate cancer and healthy controls. Significant difference was observed hemoglobin (9.15 ± 0.72, 12.83 ± 0.31 P - 0.0001*), Red blood cells (2.51 ± 1.92, 4.28 ± 0.14, P- 0.002*), WBCs (2011.54 ± 30.66, 6045.15 ± 25.24, P- 0.0001*), Platelets (1.02 ± 0.29, 4.38 ± 17.36, P- 0.0001*), Neutrophils (35.62 ± 6.49, 5.25 ± 35.07, P- 0.004*), PSA (9.68 ± 2.11, 5.13 ± 1.56, P - 0.001*) in the groups of prostatic cancer patients. Significantly higher levels of serum prostate specific antigen and decreased levels were observed in patients with prostate cancer on treatment when compared with newly diagnosed prostate cancer patients (p<0.001).

Parameter	Newly Prostate Cancer	Prostate Cancer on Treatment	P value
Age (Years)	51.63 ± 8.37	51.51±7.19	0.935
Haemo-globin	12.83 ± 0.31	9.15 ± 0.72	0.686
RBCs	4.28 ± 0.14	2.51 ± 1.92	0.513
Platelets	4.38 ± 17.36	1.02 ± 0.29	0.001*
WBCs	6045.15 ± 25.24	2011.54 ± 30.66	0.012*
Neutrophils	5.25 ± 35.07	35.62 ± 6.49	0.001*
PSA (ng/ML)	5.13 ± 1.56	9.68 ± 2.11	0.001*

Table-1. Comparison of biochemical parameters in patients with two groups of Prostate Cancer

Table - 2 shows the positive correlation of SerumPSA and complete blood count in both the groups of prostatic cancer patients.

The serum prostate specific antigens were negatively correlated with complete blood count in patients with prostatic cancer.

Table -2. Pearson Correlation in between serum PSA/PAP with Liver Function Tests

Parameter		r value	P-value
PSA	Haemoglobin	- 0.040	0.0001**
	RBCs	- 0.030	0.0001**
	Platelets	- 0 .277	0.0001**
	WBCs	- 0.236	0.0001**
	Neutrophils	-0.394	0.0001**

Discussion

Prostate-specific antigen synthesized from the epithelium of the prostate gland and secreted into the seminal fluid to maintain liquefaction of seminal fluid [17]. In circulation this will present in two major forms, complexed form bound with alpha 1-antitrypsin and another form free form. The normal serum levels of total PSA are less than 4 ng/L [18]. The measurement of serum PSA levels is useful for the early detection and progression of prostatic cancer. The present study also found significantly elevated levels of serum prostate specific antigen levels were observed in both the groups of prostate cancer patients [19]. Previous studies were done a systemic review on PSA screening, the elevated levels are useful for early detection and progression of prostate cancer when compared with the controls [20]. Based on evidence that early androgen deprivation therapy improves outcomes in certain clinical settings, many men with non-metastatic prostate cancer are treated with gonadotropin-releasing hormone agonists. Early primary androgen deprivation therapy improves survival for men with locally advanced prostate cancer. Adjuvant androgen deprivation therapy improves survival for men with locally advanced prostate cancer treated with radiation therapy, Men are with a strong family history of prostate cancer and PSA Screening can reduce the mortality from prostate cancer [21]. Men with metastatic prostate cancer and disease progression despite androgen deprivation therapy have a poor prognosis. In two recent randomized controlled trials for example, the median survival was only 16 to 18 months for men with progressive castrate metastatic prostate cancer. Recent changes in patterns of diagnosis and treatment have dramatically increased the number of men receiving gonadotropin-releasing hormone agonists for non-metastatic prostate cancer [22].

Although most of these men will eventually experience rising PSA despite castrate levels of testosterone, little is known about the natural history of men with androgen-independent prostate cancer and no radiographic evidence of metastases [23]. To the best of our knowledge, this is the first analysis to prospectively evaluate the natural history of non-metastatic prostate cancer and rising PSA despite androgen deprivation therapy [24]. Notable features of the study design include confirmation of a castrate testosterone level at study entry, documentation of PSA progression with three serial rises, and radiographic screening to exclude men with bone metastases at study entry [25]. In addition, bone scans were obtained every 4 months to minimize PSA bias in defining the primary study outcome of time to first bone metastases.

Elevation in serum PSA levels after surgery or radiation therapy for early-stage prostate cancer typically predates clinically or radiographically detectable metastatic disease by several years, without additional treatment. In a retrospective series of 315 men with a rising serum PSA after radical prostatectomy for example, the median time to first bone metastasis was 8 years from the time of PSA elevation [26-28]. Three years following initial postoperative PSA elevation, only 27% of patients had radiographically detectable metastases. The results of our study suggest that rates of disease progression remain low for men with "PSA only" prostate cancer, even after androgen deprivation therapy. Prostate adenocarcinoma proliferation is highly dependent on circulating sex steroids, specifically testosterone and dihydrotestosterone, and the binding of these hormones to receptors on prostate cancer cells.

Changes in sex steroid production, particularly decreased androgens and/or increased estrogens, can inhibit the growth and development of well-differentiated prostate cancers but may have little influence or even an undesirable effect on poorly differentiated prostate tumors [29-30]. This phenomenon has been demonstrated with finasteride, which decreases the conversion of testosterone to dihydrotestosterone by inhibition of the 5-alpha reductase enzyme. In the Prostate Cancer Prevention Trial, finasteride was found to significantly prevent or delay prostate cancer by almost 25% overall, however, the risk for having high-grade disease, specifically Gleason grade 7 to 10 tumors, was significantly increased [31].

We also analysed complete blood count in both the groups of study subjects found significantly decreased levels in patients with prostatic cancer patients with on treatment when compared to newly diagnosed prostatic patients. Similarly other some of the few studies to date analyzed systemic inflammation as a function of the black race, particularly after treatment with radical prostatectomy (RP), included 336 black patients undergoing RP with data on pre-operative CBC, found that those who had lower Neutrophils count also had higher clinical and pathological Gleason scores, indicating a high tumour grade at RP20. This study suggests continuous monitoring of serum prostate specific antigen and complete blood count useful for diagnosis and progression of prostatic cancer patients. Against this backdrop of uncertainties, risks, and potential benefits, we have developed a guideline that accentuates the importance of involving men in the decision of whether to initiate and continue testing for prostate cancer. To engage in this decision, men must have a basic understanding of the importance of prostate cancer, the potential benefits of early detection, the strengths and limitations of PSA testing, and the risks of finding and treating screen-detected cancer. In the guideline statement, we have attempted to provide the core elements of information necessary for an informed decision. How men use this knowledge will depend heavily on the value they place on the various elements: Is the opportunity to potentially lower a man's probability of dying from cancer worth the risk of deleterious effects of treatment [32]. Does the realization that some men are treated unnecessarily outweigh the reassurance that comes from finding cancer at an early stage. Previous studies also reported that biopsy samples were required to be obtained from patients with decreased neutrophils accompanied by a high level of PSA and patients with neutropenia were at a higher risk for poorly differentiated prostate cancer. In our study, we also obtained similar findings which were consistent with those reported by Although the WBC and neutrophil counts were lower in patients with prostate cancer, they did not reach statistical significance. In addition, patients with BPH had a higher level of neutrophils. Recently, however, it has been largely reported that leukocytosis as well as neutrophil-to-lymphocyte ratio and multiplied neutrophils and lymphocytes may be a diagnostic and prognostic tumor biomarker. Several studies demonstrated that the neutrophil-to-lymphocyte ratio is a prognostic factor for colorectal and non-small cell cancer [33].

Highly significant differences in the expression of genes related to immunobiology within the tumour microenvironment were identified between these two groups. This interpretation was supported by both disease association and pathway analyses. CBC, especially the systemic inflammatory parameters, contain many clues reflecting how the human mechanism works [34]. They are very helpful in the diagnosis of many diseases in addition to the physical examination findings. Recent studies have shown that CBC findings might also be used in tumoral diseases. The relationship between inflammation and cancer has been already known for decades. It has been known that some cancers develop on the ground of chronic inflammation or some infectious agents are involved in cancer etiology. However, during cancer development, inflammatory mediators play an important role in creating a microenvironment that will allow the tumour to grow and spread. Further, many studies suggest that not only the inflammatory response in the tumoral tissue but also the systemic inflammatory response is associated with the tumor prognosis [35-36]. Similar to the inflammatory cells, platelets play a role in the development of cancer. Platelets also contribute to the formation of angiogenesis by stimulating vascular and endothelial growth factors, in turn supporting cancer development [37]. Moreover, platelets play an active role in the metastatic process by facilitating the adhesion of cells to the vessels and the thrombocytosis is also associated with advanced or metastatic cancers and is regarded as a negative predictive marker for many cancers such as endometrial, cervical, ovarian, gastric, and esophageal carcinoma, and breast cancer.

Conclusion

This study suggesting that the serum Prostatic Specific Antigen (PSA) levels sensitive parameters for early detection of prostatic cancer and also for these patients frequent measurements of complete blood count useful for early detection of further complications.

What new this study adds to existing knowledge

In prostate cancers by using prostate specific antigens and prostate phosphatase were used for diagnosis and progression of prostatic cancers. But these prostate cancers leads to further complications on bone and liver, some blood-related

Metastasis, for continuous monitoring of complete blood count as well as prostate-specific antigen and prostate acid phosphatase.

Authors Contribution

Dr. Rashmi GS Basavaraj, Data collection, Literature review, Manuscript preparation, Manuscript editing, Final approval. **Dr. Ravikumar Malladad**, Patients Selection, Collection of Samples, Data Analysis and Statistical analysis.

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