International Journal of Academic Health and Medical Research (IJAHMR)
ISSN: 2643-9824
Vol. 4, Issue 4, April – 2020, Pages: 26-31

The Impact of Total PSA Value on Diagnosis of Prostate Diseases in Sudanese Patient

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Abstract: Introduction: *Measuring total serum PSA levels is currently the mainstay of prostate cancer detection and many studies have shown that patients with prostate cancer have in general high levels of serum PSA. The commonly cut-off point used for PSA is 4 ng/mL.* ***Aim:*** *The aim of this study was to determine the sensitivity and specificity of the total PSA in the diagnosis of prostate cancer also to determine its significance in diagnosis of benign prostate hyperplasia.* ***Material and methods:*** *By reviewing the medical records, clinical and laboratory information of 250 cases are collected from the archives of the El-Rahmma diagnostic center Khartoum North Sudan. Statistical analysis of the obtained data was done by IBM SPSS advanced statistics version 22 (SPSS Inc., Chicago, IL). Analysis of the ROC (receiver operating curve) was used to determine the sensitivity and specificity.* ***Results:*** *41 % of adenocarcinomas are seen between 61 to 70 years old. Gleason score grade group 3 is the most commonly diagnosed (28%), Gleason's score grade group is not statistically dependent on age at diagnosis P value (0.786). Serum tPSA with a cut-off of 4 ng/mL had 99% sensitivity and 7% specificity, statistically it is not significant for prostate cancer P.value (0.367).* ***Conclusion:*** *Total PSA was relatively significant in detection of prostate cancer and should not be used alone as a guideline without DRE. Prostatectomy should not be performed before histopathological diagnosis when the level of tPSA was above 2 ng/ml.*

Keywords: Diagnosis, Prostate, Diseases, Sudan

Introduction:

Prostate specific antigen (PSA) is a member of serine protease of the human glandular kallikrein family. It is a 34-kD glycoprotein consists of 237 amino acids with high sequence homology with human glandular kallikrein 2 (HK2). PSA is usually synthesized in the prostate ductal and acinar epithelium and is found in normal, hyperplastic and malignant prostate tissue. PSA liquefies the coagulum of seminal fluid through proteolysis of the gel-forming proteins releasing spermatozoa. It can reach the serum through diffusion from the luminal cells through the basal cell layer, glandular basement membrane and extracellular matrix . Measuring total serum PSA levels is currently the mainstay of prostate cancer detection and many studies have shown that patients with prostate cancer have in general high levels of serum PSA. The commonly cut-off point used for PSA is 4 ng/mL. In case where serum PSA levels are 4 to 10 ng/mL, the incidence of prostate cancer detection on needle biopsy in men with a normal digital rectal exam (DRE) is maximum 25%. With serum PSA concentrations higher than 10 ng/mL, the incidence of cancer on biopsy increases to 67%. However the risk of cancer is proportional to the PSA level in serum even at values less than 4 ng/mL. As large screening trials have reported that clinically significant cancers occur in men with PSA levels of 2.5 to 4.0 ng/mL thus proposed lowering the cut-off point of serum PSA to 2.5 ng/mL will improve early detection of cancer in younger men. When PSA gains access into the circulation most remains bound to serine protease inhibitors (Dabbs, 2014).

The three most recognizable inhibitors are α-1–antichymotrypsin (α1-AT), α-2–macroglobulin, and α-1–protein inhibitor. PSA bound to α1-AT is the most immunoreactive and clinically the most useful in diagnosis of prostate cancer. A smaller fraction (5% to 40%) of the measurable serum PSA is free (noncomplexed). Thus total serum PSA level measured reflects both free and complexed PSA. It has been reporteded that the percent of free PSA will improve the specificity of PSA testing for prostate cancer. Recently, additional isoforms of free PSA have been. PSA firstly secreted in the form of a precursor termed pro-PSA which is inactive form of the enzyme constitutes the majority of free PSA level in serum in men with prostate cancer making the relative increase of serum pro-PSA a risk marker of prostate cancer. Benign PSA (bPSA) refers to a cleaved form of PSA from benign prostatic hyperplasia tissue. Measurement of the ratio of pro-PSA to BPSA has been proposed as a means of improving the accuracy of cancer diagnosis in men with a very low percentage of free PSA levels who are at relatively high risk (Dabbs, 2014).

Serum total prostate specific antigen (tPSA) was found to be elevated in men with prostate cancer as 5 to 10 years prior to symptoms of clinical disease (Brawley, 2012). High PSA levels is clearly associated with an increased risk of prostate cancer. Unfortunately, PSA test is organ-specific and not prostate cancer-specific, this explains the overlap in PSA values between benign conditions as Benign Prostatic Hyperplasia (BPH), prostatitis and prostate cancer(Lamy *at al*, 2017).

However the prostate cancer prevention trial (PCPT) study reported that prostate cancer can be detected even if PSA is below 4 ng/mL, pointing out the fact that there is no PSA cut-off threshold below which the risk of detecting a prostate cancer on biopsy is zero. The choice of a PSA threshold at which a clinician may recommend a biopsy still controversial. This requires from the urologist a thorough explanation regarding the respective risks and benefits of the procedures and the possible utilization of other markers (Thompsen *et al*, 2013).

Considering the wide prescription of PSA tests for prostate cancer and the development of screening programs, more than 60% of prostate cancer were diagnosed inasymptomatic patients with normal DRE and elevated PSA (Jean-Luc, 2019). Androgens induces production of a prostatic secretory glycoproteins prostate-specific antigen (PSA) that can be used with caution to screen disease and monitor response to treatment. PSA is not specific to malignancy and will be elevated after manipulation of the prostate by digital examination. Approximately 98% of patients with metastatic prostate cancer will have elevated PSA (Anderson *et al*, 2012). However there are few cancers that are localized despite substantial elevations in PSA. Prostate specific antigen elevates in enlarged prostate gland, older age, prostatitis, ejaculation, riding a bicycle, certain urologic conditions and certain medications (Zheng *et al*, 2012). PSA decreases in 5- alpha reductase inhibitors, herbal mixtures, obesity, aspirin use, thiazide diuretic and statin. Patients with intermediate levels of PSA usually have localized and therefore potentially curable cancers. It should be remembered that approximately 20% of patients who develop radical prostatectomy for localized prostate cancer have normal levels of PSA (Nath *et al*, 2012).

Methodology:

A 250 (n = 250) patients aged from 50 to 87. By reviewing the medical records, clinical and laboratory information of all cases are collected (Serum tPSA, age and diagnosis) from the archives of the El-Rahmma diagnostic center Khartoum North Sudan. All patients in the last three years were included.

Total PSA values were recorded and three groups were formed according to the diagnosis as follow prostate cancer, benign prostatic hyperplasia and Atypical Foci Suspicious for Cancer.

Results are shown through number of cases, mean and standard deviation, range or median, frequency, percentage area under the curve (AUC), sensitivity and specificity and confidence interval (CI) as appropriate. Analysis of the ROC (receiver operating curve) was used to determine the sensitivity and specificity. All results of the analysis with $p < 0.05$ or at the level of confidence of 95% were considered statistically significant. Statistical analysis of the obtained data was done by IBM SPSS advanced statistics version 22 (SPSS Inc., Chicago, IL).

Results:

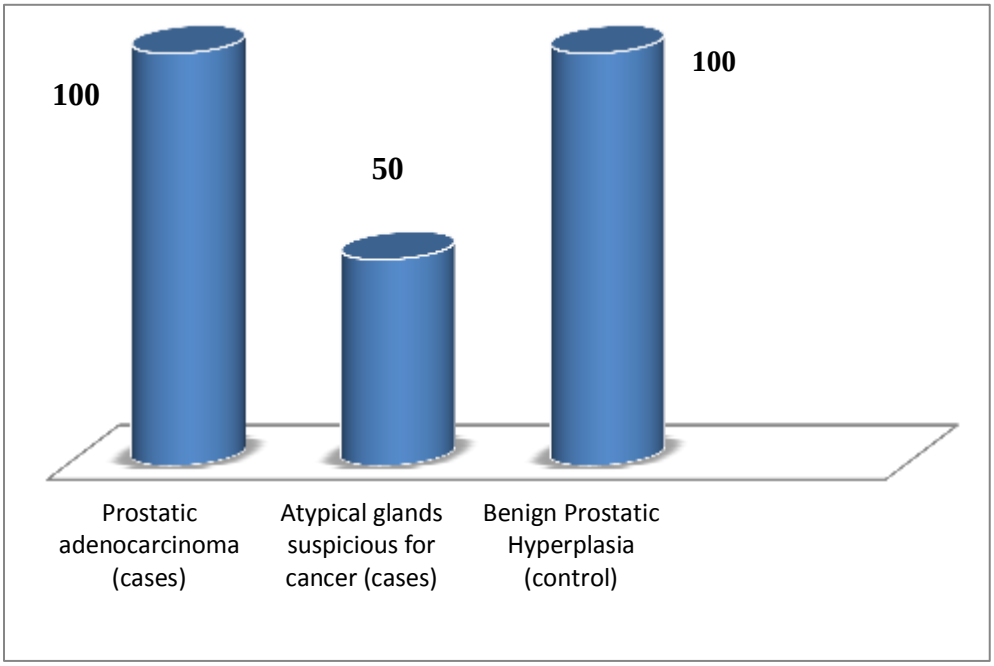

Figure (1): Distribution of study population.

Table (1):The mean and standard deviation (SD) of age/year in study population.

	No	Mean	Standard deviation	Minimum	Maximum
Prostatic Adenocarcinoma (cases)	100	67.1	8.4	50	87
Benign Prostatic Hyperplasia (control)	100	66.3	7.8	50	79
Atypical Foci Suspicious for Cancer (cases)	50	66.6	8.0	50	79

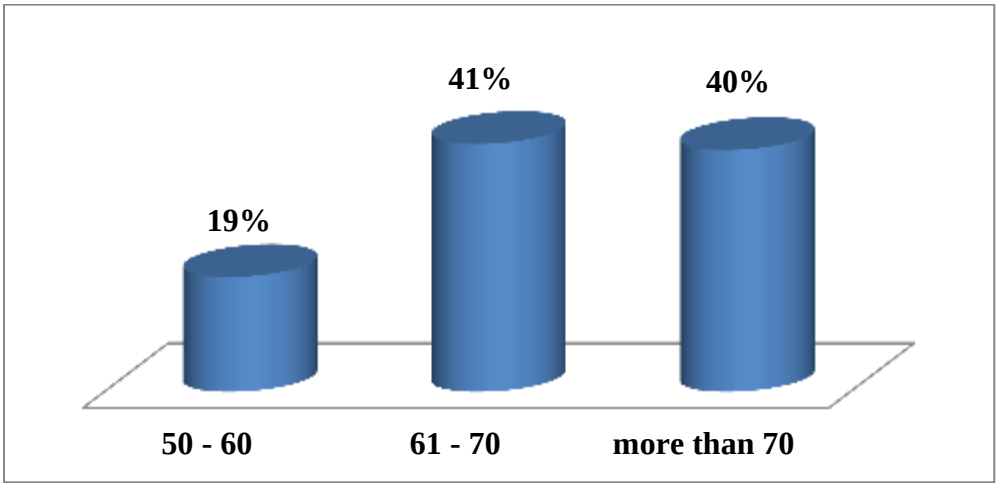

Figure (2):Distribution of prostatic adenocarcinoma cases according to age group.

Table (2) The frequency of prostatic adenocarcinoma (case) according to the Gleason grade group.

Grade group	Frequency	Percent %
1	5	5
2	21	21
3	28	28
4	22	22
5	24	24
Total	**100**	**100**

Table (3) mean, standard deviation and range of PSA.

PSA	N	Mean	Std. Deviation	Minimum	Maximum
Prostatic Adenocarcinoma	100	19.6900	10.01382	2.00	45.00
Benign Prostatic Hyperplasia	100	18.4100	10.17830	2.00	50.00
Atypical Foci Suspicious for Cancer	50	18.2600	10.42918	2.00	40.00

Table (4): The area under the curve (ROC) curve for PSA according to H & E

Variable	PSA
Classification variable	H & E
Sample size	200
Positive group [a]	100(50.00%)
Negative group [b]	100(50.00%)
Area under the ROC curve (AUC)	0.530
Significance level P (Area=0.5)	0.0293
Sensitivity	99.00
Specificity	7.00

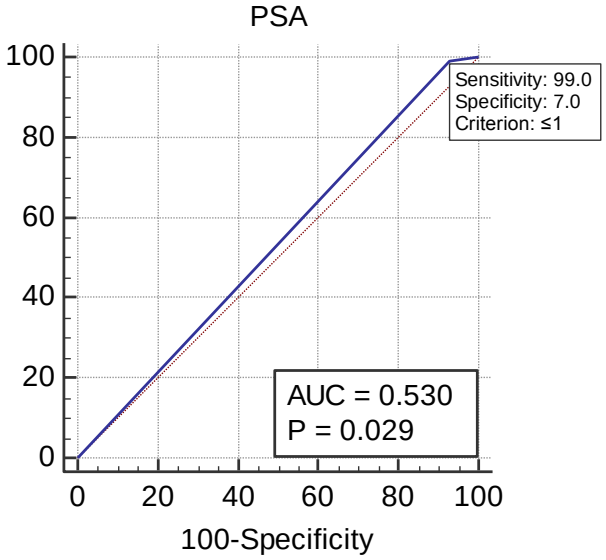

Figure (3): The sensitivity and specificity of PSA according to H & E

Discussion:

In the current study the age of patients with prostate adenocarcinoma ranged from 50 to 87 years old (Table1). This result is supported by study conducted by Epstein and Loton, 2016 which concluded that prostate cancer is typically a disease of men older than 50 years of age. However Huang *et al*, 2017 noted that prostate cancer patients younger than 50 years accounted for only 0.55% of all prostate cancer cases. Recently Emiogun *et al*, 2019 observed that the lowest age of prostate cancer patients at diagnosis was 50 years. In more details the present study clearly demonstrates that 60 % of prostate cancer cases occur at the age of 50 years old and younger than 70 years (Figure 2), the majority of them 41 (41%) are seen between 61 to 70 years old. These findings were in agreement with study in Nigeria by Emiogun *et al*, 2019 in which prostate cancer cases were most commonly seen between 61 to 70 years (42.3%). Also recent Egyptian study done by Al-Sayed *et al*, 2019 reported that prevalence of prostate cancer is predominant between 60-70 years of age and represents (40%). Regarding benign prostatic hyperplasia (BPH) in the present study, it ranges from 50 years to 79 years old (Table1). It is also a disease of older age, as revealed by previous study of Lee *et al*, 2016. In the present study the mean age of BPH is 66.3 (±7.8), this result is agreed with study done by Biswas and Talukdar 2019 in which the mean age for BHP is 62.79 (±8.67). Also the mean age of prostate cancer patients is 67.1 (±8.4) which is agreed with the 64 (±8.4) mean age reported by Yeldir *et al*, 2019 and 65.12 (±8.8) previously reported mean age by Siegel *et al*, 2014; Hariharan and Padmanabha, 2016 ; Biswas and Talukdar, 2019. Statistically, age is not helpful to differentiate between BHP and prostate cancer, p value (.743). This result agreed with that of Biswas and Talukdar, 2019.

An important highlight of the present study is the fact that Gleason score grade group 3 is the most commonly diagnosed (28%), followed by grade group 5 and grade group 4 of disease 24% and 22% respectively (Table 2). This finding is in agreement with Okolo *et al*, 2008 and Rathod *et al*, 2019 studies which observed that the commonest Gleason grade was 3 and in contrast to study in Nigeria by Oluwole *et al*, 2015 which observed that the majority of prostate cancer cases were of Gleason score of 8 (grade

group 4). On the other hand, study in Nigeria by Emiogun *et al*, 2019 shows that grade group 5 prostate cancer is the most commonly diagnosed (37.5%). However, a study in the United States reported that Gleason grade 3 was the commonest with an overall decline in scores from 8-10 to less than 6 in recent years (Gueye *et al*, 2003). A plausible explanations for the higher proportion of high grade cancers is the socioeconomic challenging in Sudan that includes absence of low cost screening programmes, late presentation to health facilities (usually patients present at advanced stages of the malignancy), lack of follow-up, and inherent social norms and beliefs. This observation is a call for the need for early detection to reduce mortality from the disease and decline noted in the United States study is as a result of improved early detection and diagnosis of prostate cancer in that country.

The result of this study shows no statistical correlation between age and Gleason score P value (0.786). This result agreed with result of Emiogun *et al*, 2019, who noted that Gleason grade is not statistically dependent on age at diagnosis.

In this study serum tPSA level in prostatic cancer ranges from 2-50 ng/ml, while in BPH it ranges from 2-40 ng/ml and it ranges from 2-45 ng/ml in atypical suspicious biopsies. The present study observed marked serum tPSA elevation in prostatic cancer, 80% of studied cases have a serum tPSA level more than 10 ng/ml this result is in agreement with findings of Baltacı and Gokçe, 2013; Baig *et al*, 2015 who reported marked elevation in serum PSA level more than 10 ng/ml in vast number of examined cases and Al-Sayed *et al*, in 2019 who found that serum tPSA levels were elevated in (76.7 %) of studied prostate cancer specimens. In this study tPSA level more than 10 ng/ml is reported in 76% of BPH cases, this result disagree with Turkish study by Ayyıldız and Ayyıldız at 2014 which reported that 50% of BPH cases have tPSA level more than 10 ng/ml this difference could be attributable to differences in ethnicity factors which may exert differences in BPH characteristics.

The present study observed overlap in PSA values between BPH and prostate cancer. This overlap indicate that PSA has a high false-positive rate leads to unnecessary prostate biopsies and over diagnosis of low-risk cancers, which may results in potential overtreatment. In this study the mean serum tPSA level in prostatic cancer is 19.6 ± 10 ng/mL and in BPH is 18.4 ± 10 ng/mL. However this result disagree with European results of Brooks *et al*, 2015 and Caliskan *et al*, 2015 who found that means of tPSA levels in prostatic cancer were 8.7 ± 8.8 ng/ml and 8.03 ± 5.21 ng/ml respectively, recently Asian study done by Hamid *et al*, 2019 observed 13.73 ± 11.44 ng/mL was the mean serum tPSA level in prostatic cancer this variation may be due to several factors such as prostate volume, urinary tract infection prostatitis and genetics.

The mean of serum tPSA levels in this study were correlated with prostate cancer to determine the relationship between tPSA and prostate cancer, the result observed that tPSA level statistically is not significant for prostate cancer (P.value 0.367) and cancer can be detected at any level. This is supported by the fact that prostate epithelial cells are responsible for circulating PSA, and elevated serum PSA is observed in men with BPH, prostatitis, or prostate cancer (Ida Bagus *et al*, 2016).

In this study the detection rates of prostate cancer within specific levels of tPSA range from 4 -9.9 ng/mL and from 10 to 19.9 were 17% and 38% respectively. This results disagree with Ida Bagus, *et al*, 2016 and Shahab *et al* 2013 who reported the prostate cancer detection rates in Indonesian men were 9.3% and 13.1%, respectively. This differences may be due to variation in population size or racial differences.

In this study, to assess the overall predictive value of tPSA, the area under the curve (AUC) in a ROC analysis have been used with a cut-off of 4 ng/mL which is the most commonly used cut off point for PSA Table (4.5). The result showed that the AUC of PSA is 0.530 which is similar to (AUC 0.530) reported by Jue *et al*, 2017. This result support the Sudanese study by Elimam and Sharfi, 2013 which concluded that the cut off point for tPSA for screening Sudanese males for prostate cancer should be lowered to 0.2 –2.1 ng/ml.

The present study reported that PSA had sensitivity of 99% and specificity of 7% which is disagree with available literature from Sudan by El Imam *et al*, 2009 that documented PSA had 91.6% and 24%, sensitivity and specificity respectively this differences may be due to methods used for measurement of PSA.

Conclusion: Total PSA was relatively significant in detection of prostate cancer and should not be used alone as a guideline without DRE. Prostatectomy should not be performed before histopathological diagnosis when the level of tPSA was above 2 ng/ml.

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