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Assessment of Prostate Specific Antigen (PSA) Level as Diagnostic Marker for Prostate Cancer in the Gezira State, Sudan

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Authors' contributions:
This research was conducted in collaboration between the two authors. The authors involved in the study design, protocol writing, results interpretation and final manuscript draft, reading and approval. Author RM S managed the field data collection. Authors AM A preformed the laboratory techniques and statistical analysis. The two authors read and approved the final manuscript.

Abstract: *The screening tests help to find cancers in an early stage when they are more easily cured. Prostate cancer can be found early by testing the amount of prostate-specific antigen (PSA) in the blood. The main objective of this study is to compare the diagnosis, sensitivity, specificity and accuracy between H&E sections and Prostate Specific Antigen (PSA) level in the diagnosis of prostate cancer. Prostate tissue (samples from the bank) was diagnosed firstly using H&E stain & a second diagnosis using Prostate Specific Antigen (PSA) Blood Test was done, finally the diagnoses were compared together. Laboratory analysis of selected 118 prostate samples showed the following: Statistically there was significant difference in the diagnosis between PSA with H&E stain (p-value=0.000<α=0.05).The benign cases with H&E include; 3 cases (3.6%) which had normal PSA level, 73 cases (88%) had moderately high PSA level and 7 cases (8.4%) although they were benign but had high PSA level. The malignant cases with H&E include; only one case (3%) although it was malignant but had normal PSA level, 16 malignant cases (47%) had moderately high PSA level and 17malignant cases (50%) had high PSA level. The equivocal case (100%) with H&E had moderately high level PSA. H&E was 94.8% sensitive, 96.4% specific, and 50% accurate. PSA test was 97.2% sensitive, 3.7% specific, and 33.1% accurate. In conclusion H&E stain is superior to PSA level for diagnosis of prostate cancer, prostate benign diseases and the equivocal cases. Also PSA level is more sensitive than H&E for all prostate diseases, but less specific and less accurate than H&E. H&E is recommended to be used for the diagnosis of prostate cancer. PSA level should be used as indicator of prostate problem particularly prostate cancer, and not specific for certain prostate disease, taking in our mind the age of the patient.*

Keywords: Prostate cancer diagnosis; H&E; PSA; Sudan

1. Introduction

Prostate cancer is one of the most common male cancers globally and in UK people account about (14%) (2016-2018) of all cancers. There are more than 200 types of cancer, but just these four types - breast, prostate, lung and bowel - together account for more than half (53%) of all new cases in the UK (2016-2018) [(1)].

Little is known about prostate cancer in Africa [(2)]. African American men have among the highest prostate cancer incidence rates in the world [(3)]. According to the data from National Cancer Registry, prostate cancer was the most commonly diagnosed cancer in men in Khartoum [(4)].

Prostatic Intraepithelial Neoplasia **(**PIN) is divided in to two grades; low grade and high grade. The transformation from low grade to high grade and invasive carcinoma is characterized by basal cell layer disruption, progressive loss of markers of secretory differentiation, and increasing nuclear and nucleolar abnormalities, proliferative activity, micro vessel density, genetic instability and DNA content [(5)]. Therefore it is postulated that PIN is derived from transformed stem cell populations located in the basal cell layer [(6)]. Low grade PIN is characterized by the presence of variable nuclear enlargement and irregular cell spacing resulting in nuclear stratification and crowding. High grade is considered the precursor of most prostate carcinoma. In high grade PIN the proliferating epithelial cells have cytologic changes mimicking carcinoma, including nuclear and nucleolar enlargement, the presence of prominent nucleoli, often multiple, is helpful in the diagnosis [(7)] [(8)]. PIN shares proliferation and differentiation disorders with other well established epithelial lesions like a typical adenomatous hyperplasia and sclerosing adenosis[(9)] [(10)] .

Early diagnosis and consequently early treatment have resulted in decreased rate of mortality among PCa patients. One of the most common tests used to diagnose PCa was introduced in 1986, when Food and Drug Administration (FDA) approved the Prostate Specific Antigen (PSA) for evaluation of the disease progression. In 1994, FDA defined the PSA concentration of 4.0 ng/ml as the upper limit of normal prostate tissue [(11)].

The Screening tests used to find the disease in people who do not have symptoms to find cancers in an early stage when they are more easily cured by testing the amount of prostate-specific antigen (PSA*)* in the blood and the digital rectal exam (DRE). Prostate-specific antigen (PSA) is a substance made by cells in the prostate gland (it is made by normal cells and cancer cells). PSA is mostly found in semen, a small amount

is also found in the blood. Most healthy men have levels under 4 nanograms per milliliter (ng/mL) of blood. A PSA is a 33-kDa glycoprotein and a member of the kallikrein family of serine proteases. It is encoded by the KLK3 gene located on chromosome 19q13.4. It is secreted by normal, hyper plastic, and cancerous prostatic epithelia. One of its roles is to degrade high–molecular-weight seminal vesicle proteins that otherwise would form seminal coagulates. Alternatively, it appears to be involved in prostate growth regulation by cleaving insulin-like growth factor–binding proteins and thereby increasing the bioavailability of these factors [(12)]. Prostate problems, such as an enlarged prostate, prostatitis or prostate cancer, can cause the PSA level to rise – but lots of other things can affect the PSA level too[(13)] .

.H&E stain is the most widely used stain in medical diagnosis. The staining method involves application of the basic dye Haematoxylin, which colors basophilic structures with blue purple hue, and alcohol- based acidic eosinY, which colors eosinophilic structures bright pink [(14)].

2. Definition Of Study And Study Area

This was a prospective, retrospective and comparison study between the ordinary histological method using H&E stain and PSA level in the diagnosis of prostate cancer. The study was conducted during the period from 2020 to 2021.

Study samples were selected from Gezira Medical Laboratory. University of Gezira, located in Gezira state, Central Sudan. These samples were brought from all over the catchment area for different techniques.

3. The Ordinary Haematoxylin And Eosin (H&E) Stain

The formalin fixed specimens of prostate samples were dewaxed, hydrated in descending grades of alcohol concentration, at 100%, 95% through 70% to distilled water for 2 minutes in each stage. For staining of the nucleus, the sections treated with Mayer's Haematoxylin for 8 minutes and differentiated by rinsing in acid alcohol for seconds, bluing in running tap water for 8minutes, counterstaining in Eosin for 1 minute, and rinsed in water. The sections dehydrated in 70% alcohol through 95% and 100% alcohol, and then blotted in a filter paper, cleared in xylene and mounted in DPX, after that the smears were ready for microscopic examination.

Interpretation of the results:

Nucleus; deep blue colour. Cytoplasm and background tissue; pink colour. RBCs; orange colour [(14)].

The results of H&E stain was evaluated according to the morphology of benign and malignant cells.

4. The Psa Level

The PSA level was recorded from the patients' documents. The result of PSA test; was graded as normal (less than 4 ng/mL) of blood, moderately high (5- 65 ng/mL), and high (more than 65 ng/mL).

5. Results

5.1. The age of the study population:

Table (5.1): Shows the age of the study population

PSA Level	Frequency	Percent
Normal	4	3.4
Moderately high	90	76.3
High	24	20.3
Total	118	100

Out of 118 cases, 4samples were less than 41 years old (3.4%). The people in the age between 41-69 years old were 50 samples (42.4%). The people over 69 years old were 64 (54.2%) (table 5.1).

Table (5.2): The histological diagnosis using H&E stained sections

Age group	Frequency	Percentage
<41	4	3.4
41- 69	50	42.4
> 69	64	54.2
Total	118	100

5.2 Histological diagnosis using H&E stained sections:

Eighty three (70.3%) samples were benign, 34 (28.8%) samples were malignant, and only one sample (0.8%) was atypical (table5.2).

Table (5.3): The results of PSA Test

Diagnosis	Frequency	Percentage
Benign	83	70.3
Malignant	34	28.8
A typical	1	0.8
Total	118	100

5.3 The results of PSA test:

The total number was 118 samples; 4 samples (3.4%) had normal PSA level, 90 samples (76.3%) had moderately high PSA level and 24 samples (20.3%) had high PSA level (table5.3).

5.4 The correlation between PSA levels with H&E diagnosis:

Three (3.6%) cases reported as benign with H&E had normal PSA level, 73(88%) benign cases had moderately high PSA level and 7 (8.4%) benign cases had high PSA level. p-value=0.000<α=0.05.

Only one (3%) case reported as malignant with H&E had normal PSA level, 16(47%) malignant cases had moderately high PSA level and 17(50%) malignant cases had high PSA level. p-value=0.000<α=0.05.

The equivocal case had moderately high level PSA (100%) (table (5.4)(5.5)).

Table (5.4): The Correlation the between PSA levels with H&E diagnosis

H&E	PSA			Total
	Normal	Moderately	High	
Benign	3 (3.6%)	73 (88%)	7 (8.4%)	83 (100%)
Malignant	1 (3%)	16 (47%)	17 (50%)	34 (100%)
A typical		1 (100%)		1 (100%)
Total	4	90	24	118

Table (5.5): The Correlation between PSA test with H&E:

Tests	Diagnosis			Chi-square (χ^2)	Degree of Freedom
	Benign	Malignant	Atypical		
H&E	83(70.3%)	34(28.8%)	1(0.8%)	86.559	2
PSA	Moderate	High	Normal	10.866	4
	90(76.3%)	24(20.3%)	4(3.4%)		

5.5 The Sensitivity, Specificity, Positive and accuracy of H&E and PSA test :

H&E was 94.8% sensitive, 96.4% specific**,** and 50% accurate. PSA test was 97.2% sensitive, 3.7% specific, and 33.1% accurate (table 5.6).

Table (5.6): The Sensitivity, Specificity, and accuracy of H&E and PSA test

Tests	Sensitivity	Specificity	Accuracy
H&E	94.8%	96.4%	50 %
PSA	97.2 %	3.7%	33.1%

5.6 The Correlation Between age of the patients and PSA level:

Out of 118cases, 4samples were less than 41years old; 2 samples had moderately high PSA level, one sample had high PSA level and one sample had normal PSA level. The people in the age between 41-69years old were 50samples; 40 samples had moderately high PSA level, 7samples had high PSA level and 3 samples had normal PSA level. The people over 69years old were 64; 48 samples had moderately high PSA level and 16 samples had high PSA level. P-value=0.001<α=0.05. (table 5.7).

Table (5.7): The Correlation Between age of the patients and PSA level

PSA	Age			Total
	<41	41- 69	> 69	
Normal	1	3	0	4
Moderate	2	40	48	90
High	1	7	16	24
Total	4	50	64	118

6. Discussion

Statistically there was significant difference in the diagnosis between PSA with H&E (p-value=0.000<α=0.05).

The benign cases with H&E include 3 cases (3.6%) which had normal PSA level, 73 cases (88%) had moderately high PSA level and 7 cases (8.4%) although they were benign but had high PSA level.

The malignant cases with H&E include only one case (3%) although it was malignant but had normal PSA level, 16 malignant cases (47%) had moderately high PSA level and 17malignant cases (50%) had high PSA level. The equivocal case (100%) with H&E had moderately high level PSA.

According to the sensitivity, specificity, and accuracy of the two methods; there was a difference between them that H&E was 94.8% sensitive, 96.4% specific, and 50% accurate. PSA test was 97.2% sensitive, 3.7% specific, and 33.1% accurate. H&E stain deal with morphology of the tissues and its staining mechanism depends on acid –base reaction between the stain and the tissues. In PSA level there were no certain rules for the elevation of PSA level and may be affected by any prostate disease specially the cancer, also may be affected by obesity and the instruments that used for testing the prostate gland or for treatment like catheter for the urinary out flow.

There was relation between the age and the PSA level (p-value=0.001<α=0.05), that the PSA level increasing with the age, may be due to decreasing in the immunity and poor health in the older people, or may be elevation of PSA is normal tissue process in the older people.

These results agree with American Cancer Society (2021), They published that most healthy men have levels under 4 nanograms per milliliter (ng/mL) of blood. The chance of having prostate cancer goes up as the PSA level goes up. When prostate cancer develops, the PSA level usually goes above 4. Still, a level below 4 does not mean that cancer isn't present, about 15% of men with a PSA below 4 will have prostate cancer on biopsy. Men with a PSA level in the borderline range between 4 and 10, have about a 1 in 4 chance of having prostate cancer. If the PSA is more than 10, the chance of having prostate cancer is over 50% (15).

The PSA test helps in the early detection of prostate cancers, but another important issue is that it can't tell how dangerous the cancer is. There are many factors to take into account, including the age, Benign prostatic hyperplasia (BPH), Prostatitis, also ejaculation can cause the PSA to go up for a short time, and then go down again, Certain medicines and Obesity(15).

Sabrina Felson, MD (2021), published that If the PSA results are in the borderline range (4 to 10), the percent of free PSA can be useful in helping to distinguish between prostate cancer or benign prostatic hyperplasia (BPH). The pattern is the opposite of that seen with PSA in that a high percent of free PSA above 20%, points to BPH, while a percent free PSA less than 10% indicates a greater likelihood of cancer (16).

Metts JC, Anthony CT, and Steiner MS (1995), found that the secretory cells contribute wide variety of products to the seminal plasma. PSA and PAP (prostatic alkaline posphatase) are produced by the secretory cells of all zones. Pepsinogen II and tissue plasminogen activator are produced only in the ducts and acini of the central zone (17).

Prostate Cancer UK (2021), published that the PSA test can miss prostate cancer; one major study showed that 1 in 7 men (15 per cent) with a normal PSA level may have prostate cancer, and 1 in 50 men (two per cent) with a normal PSA level may have a fast-growing cancer (18).

Aaron L et al, (2016), found that The PSA test is a blood test that measures the amount of prostate specific antigen (PSA) in the blood. PSA is a protein produced by normal cells in the prostate and also by prostate cancer cells. It's normal to have a small amount of PSA in the blood, and the amount rises slightly with age and enlargement of the prostate. A raised PSA level may suggest there is a prostate problem, but not necessarily cancer (19).

7. Conclusion

H&E stain is superior to PSA level for diagnosis of prostate cancer, prostate benign diseases and the equivocal cases. Also PSA level is more sensitive than H&E for all prostate diseases, but less specific and less accurate than H&E.

Due to its superiority, H&E is recommended to be used for the diagnosis of prostate cancer. PSA level should be used as indicator of prostate problem particularly prostate cancer, and not specific for certain prostate disease, taking in our mind the age of the patient.

Ethical Approval

Tissue blocks were used (the samples from the Bank), numbered samples, no patients' name.

Ethical approval for this study was obtained from the research ethical committee from the Gezira State Ministry of Health.

Competing Interests

Authors have declared that no competing interests exist.

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