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Diagnostic Efficacy of grey-zone Serum Prostate Specific Antigen level in patients with Benign Prostatic Hyperplasia and Prostate Carcinoma

Syed Atif Hussain, Rukhsana Tumrani, Afsheen Nigar, Anber Rahim, Mahnoor Chaudhry, Seerat Fatima Tu Zahra

ABSTRACT:

Objective: Evaluation of diagnostic role of grey zone serum prostate specific antigen level(4-10ng/ml) in patients with benign prostatic hyperplasia (BPH) and prostate carcinoma keeping histopathology as gold standard.

Study design and setting: Cross-sectional study conducted in Department of Urology and Chemical Pathology, Sheikh Zayed Hospital Rahim Yar Khan.

Methodology: Patients with grey zone serum prostate specific antigen level (4-10ng/ml), lower urinary tract symptoms or abnormal DRE (digital rectal examination) were included and diagnosis was confirmed on the basis of histopathology. Chi square test used to see the statistically significant difference between subgroups. P value <0.05 was deemed as significant. Diagnostic role evaluated by ROC curve analysis.

Results: Mean age of study subjects was 60.21±10.046 years and 155 (81.2%) subjects were having serum prostate specific antigen level in grey zone (4-10ng/ml). Of the total 191 study subjects, 59(30.9%) were histopathologically confirmed cases of benign prostatic hyperplasia and 34(17.8%) were confirmed cases of prostate carcinoma. 41 (26.45%) cases of benign prostatic hyperplasia were having serum PSA level in grey zone (4-10ng/ml) and 16(10.32%) cases with prostate carcinoma were having PSA level in grey zone (4-10ng /ml). ROC curve analysis shows AUC=0.584 in case of BPH and AUC=0.707 in case of CA prostate.

Conclusion: On the basis of our study, it is concluded that grey zone serum PSA level in symptomatic individuals should be used in conjunction with other non-invasive diagnostic and clinical parameters to improve diagnosis and to avoid unnecessary biopsy in every symptomatic individual.

Key words: Benign Prostatic Hyperplasia; BPH; Grey zone PSA; Prostate specific antigen; Prostate carcinoma; Serum PSA

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INTRODUCTION:

Both cancerous and normal prostate epithelial cells release PSA, a serine protease linked to kallikrein. [1] Serum Prostate specific antigen level is non-invasive marker for the management of patients with prostate enlargement. By using PSA as a noninvasive screening biomarker, the number of patients with metastatic cancer can be decreased by improving the early detection of the disease. [2, 3] PSA is specific to the prostate but not to prostate carcinoma; therefore, its use as a diagnostic tool for prostate adenocarcinoma is debatable because of its increased presence in other lesions and procedures like ejaculation, digital rectal examination, benign prostatic hyperplasia, urinary tract infections, acute and chronic prostatitis, and urethral instrumentation.[4] To lower death rates from prostate cancer, early diagnosis is crucial. One of the finest diagnostics for prostate cancer early detection is the serum prostate-specific antigen (PSA) test. As a result, many people today utilize this noninvasive test to screen for prostate cancer, especially among older men. However, even while PSA levels have a high sensitivity for detecting prostate cancer, they lack sufficient specificity

when PSA levels are relatively low, as they do in the 4–10 ng/mL "gray zone." Elevated PSA levels in progressing carcinoma can be utilized as a prognostic tool; the values are adjusted for age and race. [5]

Urgent attention is needed to increase the detection rates of prostate cancer and to prevent unnecessary prostate biopsies in men whose PSA levels are in the gray zone. [6, 7]When the PSA level is in the gray area, it's critical to research the associated factors that lead to a positive biopsy result for Prostate carcinoma. The two related parameters that are currently most frequently employed to determine the positive rate of prostate biopsies are PSA density (PSAD) and the ratio of free to total PSA (f/tPSA). Still, there are issues with clinical prediction. It is widely acknowledged that prostate cancer typically develops in the prostate's peripheral zone, whereas lesions associated with benign prostatic hyperplasia (BPH) are primarily found in the core gland. [8, 9]

It is vital to assess the clinical importance of different PSAs and PSA density (PSAD) connected to peripheral zones in patients with gray zone PSA level (4–10 ng/mL) because the limited specificity of PSA leads to needless and invasive prostate biopsies. [10, 11]

An increasing percentage of prostate cancers, primarily indolent disease, have been identified early because to the widespread use of prostate specific antigen (PSA) in screening techniques. The availability of several treatment approaches, each of which has a distinctly different effect on the patient's quality of life, indicated that there was a clear need for instruments capable of identifying clinically significant malignancy at diagnosis. When it came to pre-biopsy diagnosis, multiparametric magnetic resonance performed incredibly well. It does, however, require an experienced radiologist and is a costly technology. It is worthwhile to look into a straightforward blood test in this situation. Under these circumstances, scientists concentrated on creating a lab test that may reduce overdiagnosis without compromising the ability to identify malignant tumors. [12]

The study aims to evaluate grey zone serum prostate specific antigen level in patients with lower urinary tract symptoms and abnormal digital rectal examination and to evaluate the diagnostic efficacy of grey zone serum prostate specific antigen (PSA) level in patients diagnosed with benign prostatic hyperplasia (BPH) and prostate carcinoma. The implication will be that by evaluating the diagnostic role of non-invasive screening biomarker serum prostate specific antigen (PSA) level help to prevent unnecessary invasive biopsies in patients with abnormal digital rectal examination and it will help in early detection and management of patients with metastatic disease.

METHODOLOGY:

Cross-sectional study conducted in Department of Urology and Chemical Pathology, Sheikh Zayed Hospital Rahim Yar Khan from January 2022 to December 2023. After taking ethical approval from institutional review board (Ref no. 239/IRB/SZMC/SZH Dated 25-11-2021), data was collected by using non-probability consecutive sampling technique. Patients with grey zone serum prostate specific antigen level (4-10ng/ml), lower urinary tract symptoms or abnormal DRE (digital rectal examination) were included and informed consent was taken. Histopathology was taken as gold standard to confirm the diagnosis of prostate carcinoma and benign prostatic hyperplasia. Patients with history of prostate surgery, hormonal manipulation, history of taking 5 alpha reductase inhibitor, urinary tract infection, indwelling urinary catheter and acute or chronic bacterial prostatitis were excluded. Sample size calculated by using formula ($n=z^2x\ p\ (1-p)/E^2$) where z is z score, p is proportion of population having PSA level in grey zone and E is margin of error. Confidence interval is taken as 95% and z score value is 1.96 for 95% confidence interval. Margin of error is calculated as 7% by using the sample size 197 and proportion as 41%. So, the sample size(n) calculated as 190 by using p (the proportion of subjects having PSA level in grey zone taken as 41%).[24] Data was analyzed by using SPSS version 29. Mean and SD calculated for quantitative variables (Age, Serum PSA level) while frequency and percentages calculated for qualitative variables (Prostate carcinoma, Benign prostatic hyperplasia). Effect modifier (age) controlled through stratification. Post stratification chi square test is applied to see the statistically significant difference. Statistically significant difference of grey zone serum PSA level with respect to benign prostatic hyperplasia and prostate carcinoma is evaluated by applying chi square test. P value <0.05 was taken as statistically significant. Diagnostic role is evaluated by ROC curve analysis. Sensitivity and specificity of grey zone PSA level (4-10ng/ml) calculated in benign prostatic hyperplasia and prostate carcinoma by using formulas;

Sensitivity= True positive/True positive+ False negative

Specificity= True negative/ True negative+ False positive[14]

- True positive= Number of cases correctly identified as diseased (Histopathologically confirmed cases with total serum PSA level in grey zone)
- True negative= Number of cases correctly identified as non-diseased (Histopathologically not confirmed serum total PSA level not in grey zone)
- False positive= Number of cases incorrectly identified as diseased (Histopathologically not confirmed with PSA level in grey zone)
- False negative= Number of cases incorrectly identified as non-diseased (Histopathologically confirmed with PSA level not in grey zone)

RESULTS:

Mean age of the study subjects was 60.21±10.046 years and 93(48.7%) were =60years age and 98 (51.3%) were above 60 years with age range 39 to 82 years (Table 1). Of the total 191 study subjects, 155 (81.2%) subjects were having serum PSA level in grey zone (4-10ng/ml) while 36 (18.8%)

were not having PSA level in grey zone (Table 1). 59 (30.9%) were histopathologically confirmed cases of benign prostatic hyperplasia and 34(17.8%) were confirmed cases of prostate carcinoma. 80 (51.61%) subjects =60years of age were having serum PSA level in grey zone while 13 (36.11%) were not having serum PSA level in grey zone (Table 1). 75 (48.38%) subjects >60years age were having PSA level in grey zone while 23 (63.88%) subjects were having PSA level not in grey zone (Table 2). The difference of grey zone PSA level with respect to age subgroups was not statistically significant with p value 0.094 (Table 2). Of the total 59 study subjects with benign prostatic hyperplasia, 41 (69.49%) were having serum PSA level in grey zone while 18(30.50%) were not having serum PSA level in grey zone (Table 2). Of the total 34 study subjects with Prostate carcinoma, 16 (47.05%) were having serum PSA level in grey zone while 18 (52.94%) were not having serum PSA level in grey zone (Table 2). ROC curve for grey zone serum PSA level in Benign Prostatic Hyperplasia shows Area under the curve (AUC=0.584) (Fig 1) while ROC curve for grey zone serum PSA level in Prostate carcinoma shows Area under the curve (AUC=0.707) (Fig 2). Sensitivity of grey zone serum PSA level in case of benign prostatic hyperplasia calculated as 26.45% while specificity calculated as 50%. Sensitivity in case of prostate carcinoma for grey zone serum PSA level calculated as 10.32% while specificity calculated as 50%.

Table 1: Distribution of study subjects with respect to age, serum PSA level (Grey zone PSA), Benign Prostatic Hyperplasia and Prostate Carcinoma (n=191)

Variable	Subgroups	Frequency	Percentage
Age (Years) 60.21±10.046	=60years	93	48.7
	>60years	98	51.3
Serum PSA level (ng/ml) 9.1067±8.457	Gray zone	155	81.2
	No Gray zone	36	18.8
Benign Prostatic Hyperplasia (BPH)	Present*	59	30.9
	Absent	132	69.1
CA Prostate	Present*	34	17.8
	Absent	157	82.2

Figure 1: ROC Curve for Grey Zone PSA level in BPH (AUC=0.584)

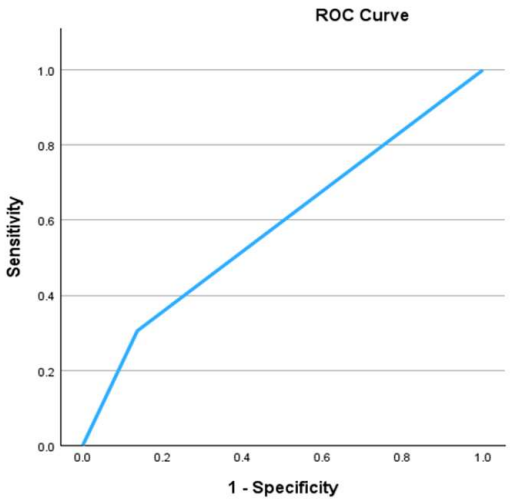

Figure 2: ROC curve for Grey Zone PSA level in CA Prostate (AUC=0.707)

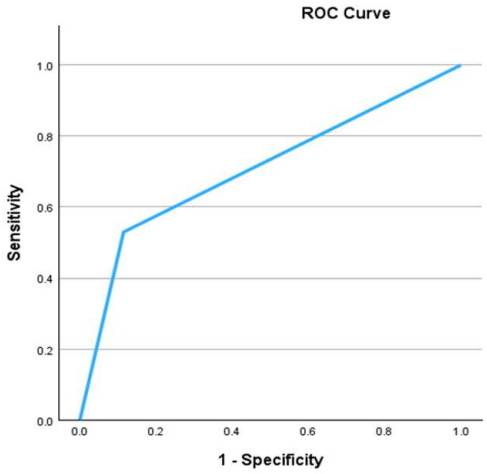

Table 2: Cross tabulation of Age, Benign Prostatic Hyperplasia and CA Prostate with respect to Grey Zone PSA level (n=191)

Variable	Subgroups	PSA level		Chi square value	*P* value
		In Gray zone	Not in Grey zone		
Age	=60 years	80 (51.61%)	13 (36.11%)	2.810	0.094
	>60years	75 (48.38%)	23 (63.88%)		
	Total	155(100%)	36 (100%)		
Benign Prostatic Hyperplasia	Present	41 (26.45%)	18(50%)	7.589	0.006*
	Absent	114 (73.54%)	18(50%)		
	Total	155 (100%)	36(100%)		
CA Prostate	Present	16(10.32%)	18(50%)	31.43	<0.001*
	Absent	139(89.67%)	18(50%)		
	Total	155(100%)	36(100%)		

**p value <0.05 taken as statistically significant*

Sensitivity (BPH) = 41/41+114 =26.45%

Specificity (BPH) =18/18+18=50%

Sensitivity (CA prostate) =16/16+139=10.32%

Specificity (CA Prostate) =18/18+18=50%

DISCUSSION:

Serum prostate specific antigen is valuable, non-invasive marker for screening prostate carcinoma but the intermediate PSA level make it difficult to discriminate between benign and malignant prostate conditions. In these conditions, many patients are subjected to unnecessary biopsies to make a definitive diagnosis. [13, 15] So, the grey zone level of serum total PSA evaluated in our study with mean PSA level 9.1067±8.457ng/ml. Of the total 191 study subjects, 155(81.2%) were having serum PSA level in grey zone while 36 (18.8%) were having serum PSA level not in grey zone. Diagnostic efficacy of serum PSA level in grey zone established for prostate carcinoma with AUC (0.707), sensitivity 10.32%, specificity 50%. Distribution of prostate carcinoma patients with respect to grey zone serum PSA level was statistically significant with p value <0.001. Diagnostic efficacy of serum PSA level established for benign prostatic hyperplasia with AUC (0.584), sensitivity 26.45% and specificity 50%. Distribution of benign prostatic hyperplasia patients with respect to grey zone serum PSA level was found statistically significant with p value 0.006.

Diagnostic efficacy of total serum PSA evaluated by Wu B et al in their study and AUC by ROC analysis was 0.508 for grey zone PSA level (p value <0.001) and for total PSA overall AUC 0.699 (P value 0.012). Mean age of study subjects in their study was 67.5±7.9 years with median total PSA level 7.94ng/ml with statistically significant difference of median total PSA level in prostate carcinoma and non-carcinoma patients (p value 0.001). [16] Screening of prostate carcinoma has important role in the management of carcinoma and clinically significant prostate cancer with PSA level in grey zone (4-10ng/ml) should have proper screening by other diagnostic tools such as prostate health index density, prostate health index and % of free prostate specific antigen to avoid unnecessary biopsies.[16, 17]On the basis of previous literature, it has been shown that many of the patients undergoing unnecessary biopsies based on serum total PSA results.[18, 19]

A single centered study conducted by Castro et al at PSA cut off 3ng/ml established the sensitivity 1.000 and specificity 0.017 with mean PSA level in cancer patients 7.50±1.70ng/ml and mean PSA in benign prostatic hyperplasia was 6.29±1.81ng/ml. [20] Another study conducted by Vukovic et al established the sensitivity of serum PSA level at cut off 3ng/ml as 0.923 and specificity as 0.063 with mean serum PSA level in cancer patients 5.81±1.98ng/ml and mean PSA level in benign prostatic hyperplasia as 6.24±1.96ng/ml. [21]

On the basis of previous literature search, it is recommended that in asymptomatic individuals with PSA level in grey zone (3-10ng/ml) and normal digital rectal examination should be evaluated further by non-invasive tools for indication of biopsy such as risk calculation, magnetic resonance imaging and if PSA doubling time is less than 3 years then it is strongly recommended that MRI should be repeated and biopsy should be performed.[22] Liu J. et al In their study evaluated the use of clinical parameters to predict prostate carcinoma in patients with total PSA level in grey zone (4-10ng/ml). On the basis of their study, the total serum PSA level didn't show significant difference in carcinoma and non-carcinoma patients with p value 0.824. Other parameters such as age, free PSA, f/t PSA also show no significant difference between carcinoma and non-carcinoma patients, however, prostate volume and PSA derivatives show significant difference with p value <0.05. It was concluded that in patients with grey zone serum PSA level, prostate volume, PSA derivatives and MRI should have been used to predict prostate carcinoma and to prevent unnecessary prostate biopsies. [23]

Our study had certain limitations. It was a single centered study. Different prostate specific reference ranges (cut-off) should have been evaluated with respect to age as age specific reference ranges are being used for interpretation of total PSA results and diagnostic efficacy should be established for each cut-off value with respect to age.

Further larger studies should be performed to further evaluate the patients with PSA results in grey zone (4-10ng/ml) by using different non-invasive investigations and clinical parameters to improve the diagnostic value and preventing the unnecessary biopsies.

CONCLUSION:

On the basis of our study, it is concluded that grey zone serum PSA level (4-10ng/ml) in symptomatic individuals with lower urinary tract symptoms and abnormal digital rectal examination should be used in conjunction with other non-invasive diagnostic and clinical parameters to improve diagnosis and to avoid unnecessary biopsy in every symptomatic individual.

Authors Contribution:
Syed Atif Hussain: Concept, design, final approval
Rukhsana Tumrani: Data analysis, manuscript writing
Afsheen Nigar: Data analysis, discussion
Anber Rahim: Data collection
Mahnoor Chaudhry: Discussion, Data interpretation
Seerat Fatima Tu Zahra: Proof reading, data analysis

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