European Journal of Molecular & Clinical Medicine
ISSN 2515-8260 Volume 08, Issue 02, 2021

Correlation Between Serum Prostate-Specific Antigen Level With Pathological Grade And Risk Of Bone Metastasis In Prostate Cancer Patients

Alaa Abdel Hamid Fayed [1], Seham Mohamed El Hagrasy [1], Abdelmonem Nasreldin Abdelmonem Hamad [1], Doaa Abdel Rahman Mandour [2]

[1]*Department of Clinical Oncology & Nuclear Medicine, Faculty of Medicine, Zagazig University, Egypt*

E-mail:abdelmenemhamad@yahoo.com

ABSTRACT

Background: Prostate cancer is most frequently diagnosed cancer of men and bone is the most common site of metastasis. There is a lack of consensus for the selection criteria for bone scan in low-risk patients. Serum prostate-specific antigen (PSA), which is produced by all types of prostate tissue, is one of the most important biomarkers for detecting prostate cancer, guiding decisions about biopsies of the prostate and offering a way to monitor disease progression.
Objective: The aim of this study is to correlate between PSA levels at the time of diagnosis, aggressiveness (Gleason score > 7) and bone metastasis of histologically proved prostate cancer patients.
Patients and methods: This study was a Cross Sectional retrospective study collected from medical records at cancer registry archive of Clinical Oncology and Nuclear Medicine at Zagazig University Hospital from January 2014 till January 2019 on 86 prostatic cancer patients with bone metastasis
Results: Mean PSA was 217.11±92.56 with range of (100.2 – 502.3), <10 was present in 8.1% of cases, 10-20 was present in 19.8%, 20-100 was present in 34.9% and >100 was present in 37.2% of cases. There was significant relation between PSA and orchidectomy ($p<0.001$), there was high significant relation between bone metastasis, PSA level ($p<0.001$) and type of PSA level ($p<0.001$) and there was significant positive correlation between PSA and GS score, bone metastasis, orchidectomy and ADT.
Conclusion: There was strong association between the PSA level, tumor aggressiveness 9 Gleason score), and bone metastasis has been identified in patients already diagnosed as cancer prostate.

Key words: Prostate Cancer, Bone Metastasis, prostate-specific antigen (PSA)

1. INTRODUCTION

Prostate cancer is most frequently diagnosed cancer of men and bone is the most common site of metastasis. There is a lack of consensus for the selection criteria for bone scan in low-risk patients. Western guidelines do not recommend use of bone scan in asymptomatic

patients and in low prostate-specific antigen (PSA) values. An indian trial correlate the PSA value with bone metastases through bone scan in the Indian population [(1)].

The common tools for diagnosis of prostate cancer are the digital rectal examination (DRE) and a serum prostate-specific antigen (PSA) test.Even though PSA levels between 0-4 ng/ml is generally accepted as normal range, there is no world widely accepted cut-off value. Different grouping scales were defined for preoperative PSA levels. But the most commonly used one is low-risk (PSA<10 ng/ml), medium-risk (PSA 10-20 ng/ml) and high risk (PSA>20 ng/ml). PSA level is most commonly used for determining patients to whom needle biopsy should be performed. However, many studies point out the PSA level may also correlate with the biological aggressiveness of the tumor [(1)].

Serum prostate-specific antigen (PSA), which is produced by all types of prostate tissue, is one of the most important biomarkers for detecting prostate cancer, guiding decisions about biopsies of the prostate and offering a way to monitor disease progression [(2)].

Because free PSA (fPSA) became a biomarker identification, PSA has a high sensitivity but a low specificity, which can result in unnecessary biopsies, especially in patients with benign disease, and cancers overlap when the tPSA is moderately elevated. Because the free/total (f/t PSA) ratio appears to be most clinically useful when PSA reaches levels of 4 to 10ng/mL, detecting the free/total (f/t PSA) ratio can improve the specificity in monitoring prostate cancer and decrease the number of negative biopsies in patients [(2)].

However, F/t PSA ratio determination has a low sensitivity and specificity for the diagnosis of prostate cancer; it would not be specific or sensitive enough to use on its own. The results of the f/t PSA ratio must always be combined with other established diagnostic methods [(2)].

PSA screening helps diagnosis at earlier stages, improved outcomes after treatment, and lower mortality. However, important shortcomings of PSA screening include unnecessary biopsies due to false-positive PSA tests, over diagnosis of some clinically insignificant cancers, and potential side effects from prostate biopsy and/or prostate cancer treatment [(3)].

The high sensitivity and low specificity of PSA testing in the diagnosis of prostate cancer is a problem in clinical practice. Use of PSA testing alone has reduced specificity owing to the influence of prostate volume and other factors suchas infection and manipulation [(4)].

Even with this disadvantage, however, PSA measurement is still used in clinical practice given that no new biomarkers are currently accepted for the diagnosis of prostate cancer. The general cutoff for the PSA level is 4.0 ng/mL. With the use of this cutoff, the cancer detection rate ranges from 35% to 42.3% for 10- to 12-core biopsy. A higher PSA level may relate to a greater likelihood of positive tissue diagnosis, a higher Gleason score, and a greater likelihood of bone metastasis [(4)].

Lojanapiwat et al. [(5]. studied the correlation and diagnostic performance of the PSA level with cancer diagnosis, aggressiveness of prostate cancer (Gleason score>7), and bone metastasis. They showed a strong correlation of PSA level with tumor diagnosis, tumor aggressiveness, and bone metastasis. The prevalence of prostate cancer in this cohort was 35.39%. The chance of diagnosis of prostate cancer was greater than that for benign prostatic hyperplasia when the PSA level was higher than 20 ng/mL

2. PATIENTS AND METHODS

A total number of 86 subjects were included in this Cross Sectional retrospective study after fulfillment of the inclusion and exclusion criteria, this study was conducted from January 2014 till January 2019 in outpatient clinics at cancer registry archive of Clinical Oncology and Nuclear Medicine at Zagazig University Hospital on 86 prostatic cancer patients with bone metastasis.

Our Inclusion criteria were: Medical records of patients with patients who were histologically diagnosed as cancer prostate, aged above 50 years old, baseline serum PSA level, baseline bone scan, history of treatment for prostate cancer and who had PS 0-2.
Our exclusion criteria were: Patients who were not previously treated, who have history of malignancy an patients who had PS >3.

3. METHODS:

This study was approved by the local ethical committee of Zagazig university hospitals. Written knowledgeable consent was taken from patients or their first-degree relatives.
First for clinical assessment: all data were collected from medical records as regard: age, sex, residency, occupation, or, presence of comorbidities, such as diabetes mellitus or hypertension were evaluated, clinical examination and data collected from medical records, the patients' demographic data such as age, PSA level, details of the pathologic report such as a positive diagnosis of cancer, Gleason score, and the result of the bone scan were recorded.
For Laboratory and radiological assessment: the serum concentration of PSA and bone scan reports were collected from medical records.

4. ETHICAL APPROVAL:

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national). Institutional Review Board (IRB) of the Faculty of Medicine, Zagazig University approved the study protocol. An informed consent was obtained from all participants or their first-degree relatives and they were told about the aim of the study, and were informed that the data would be used for scientific purposes only.

5. STATISTICAL ANALYSIS

Analysis of data was done using Statistical Program for Social Science version 20 (SPSSInc. Chicago, IL, USA). Quantitative variables were described in the form of mean and standard deviation. Qualitative variables were described as number and percent. Qualitative variables were compared using chi-square (X2) test or Fisher's exact test when frequencies were below five. Pearson correlation coefficients were used to assess the association between two normally distributed variables. When a variable was not normally distributed, A P value < 0.05 is considered significant.

6. RESULTS

Mean age of studied cases was 66.53±7.21 with range of (50-78) years, mean GS score was 7.11±1.5 with range of (5-10). **(Table 1).**
Mean PSA was 217.11±92.56 with range of (100.2 – 502.3), <10 was present in 8.1% of cases, 10-20 was present in 19.8%, 20-100 was present in 34.9% and >100 was present in 37.2% of cases (**Table 2).**
There was high significant relation between PSA level and ADT **(Table 3),** there was high significant relation between bone metastasis and PSA level **(Table 4),** there was significant relation between type of bone metastasis and PSA level **(Table 5).**
There was significant positive correlation between PSA and GS score, bone metastasis, orchidectomy and ADT **(Table 6).**

Table (1) Demographic data of the studied cases:

Variable	
Age (Years):	
Mean ± SD Range	66.53±7.21 50-78
GS score:	
Mean ± SD Range	7.11±1.5 (5-10)

Table (2) PSA Level of the studied cases:

Variable	**Before treatment**		**After treatment**		**Paired T test**	**P value**
PSA:						
Mean ± SD Range	217.11±92.56 10.2 – 502.3		111.09±32.8 9.1 – 132.1		10.7	**<0.001 (HS**
PSA:	NO.	%	NO.	%	X^2	**P value**
<10	7	8.14	40	46.51	12.3	**<0.001**
10-20	17	19.77	30	34.88		**(HS)**
21-100	30	34.88	10	11.63		
>100	32	37.21	6	6.98		

Table (3) Relation between PSA level and ADT:

Variable	**ADT N=60**	**No ADT N=26**	**T test**	**P value**
PSA:				
Mean ± SD	101.19±84.11	201.12±91.01	-4.936	**<0.001 (HS)**

Table (4) Relation between PSA level and orchidectomy:

Variable	**Yes N=20**	**No N=66**	**T test**	**P value**
PSA:				
Mean ± SD	112.93±34.11	159.08±31.11	-5.683	**<0.001 (HS)**

Table (5) Relation between PSA level and type of bone metastasis:

Variable	**Single N=15**	**Multiple N=35**	**T test**	**P value**
PSA:				
Mean ± SD	**101.01±31.01**	**168.11±34.01**	**-6.556**	**<0.001 (HS)**

Table (6) Correlation between PSA level and different variables:

Variable	PSA	
	r	**P**
GS score	-0.337	**0.003 (S)**
Bone metastasis	0.321	**0.002 (S)**
Orchidectomy	0.311	**0.042 (S)**
ADT	**0.301**	**0.046 (S)**

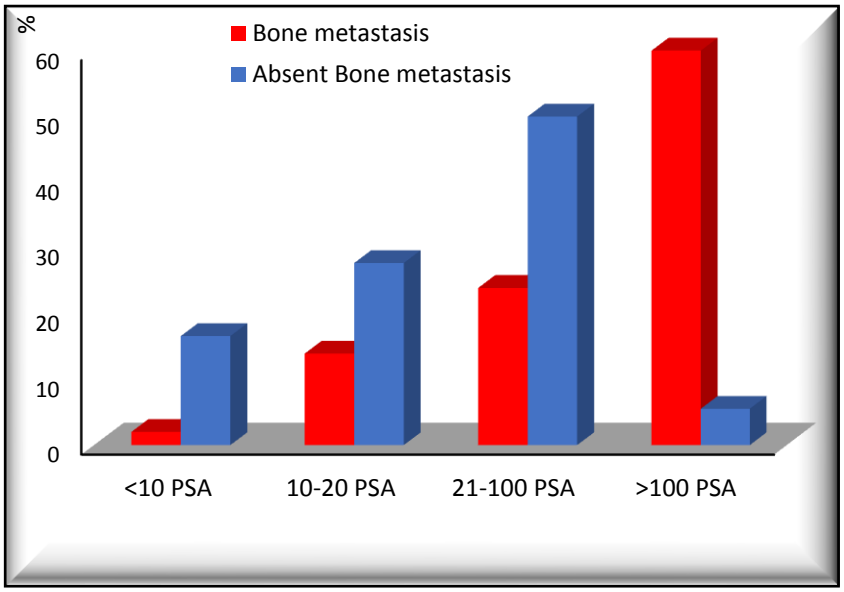

Figure (1): A complex diagram showing Mean PSA level among cases with bone metastasis and non-metastastatic cases.

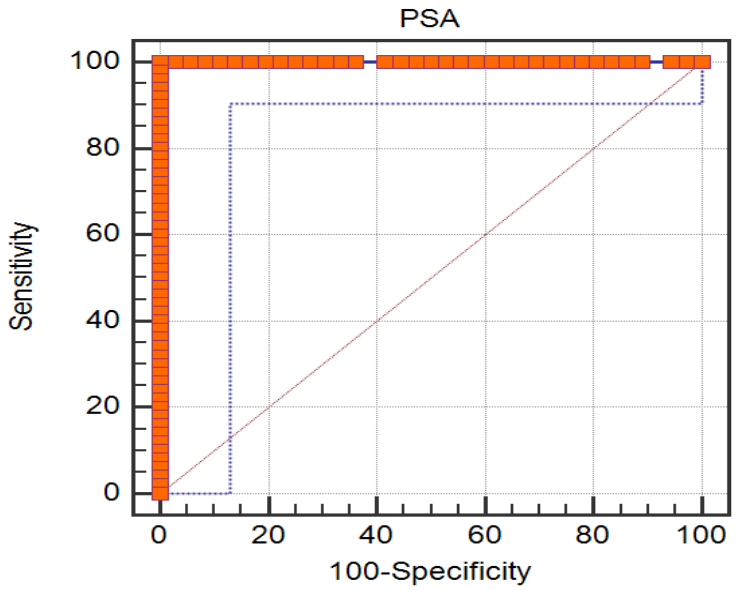

Figure (2): ROC curves showing predictive capability of PSA in bone metastasis.

7. DISCUSSION

PSA is a surrogate marker of systemic progression and cancer specific survival (CSS). Most prediction models define high risk PCa as a presenting PSA level of >20 ng/mL. However, the ability of an extremely high PSA level to reflect disease burden and its prognostic impact on survival has not been well described. Given the relationship between elevated PSA levels and inferior survival outcome, the concern about poorer outcome further intensifies when the PSA values are extremely elevated [6].

Findings of our study are in agreement with study of Lojanapiwatet al. [7] as they found that the patients' average age was 68.02 ± 8.23 years (range, 42–93 years). According to Singh et al. [8], the patients were of age 53–89 years, with mean age of 68.41 ± 7.5 years. The mean biopsy Gleason score was 7.28 ± 1.7 (ranging from 5 to 10).

Our results are supported by study of Lojanapiwatet al. [7] as they reported that the average PSA level for biopsy was 102.45 ng/mL (range, 1–5,000 ng/mL). Regarding Pai et al. [9], 53 patients (73.61 %) out of the 72-patient shad an elevated PSA level above 4ng/ml. The elevated PSA in these patients ranged from 15.1 to >100ng/ml.

Furthermore, Singh et al. [8] revealed that the mean (range) and median preoperative serum PSA in these patients were 17.98 (0.3-68.3) ng/ml and 12.1 ng/ml, respectively.

The present study showed that there was high significant relation between PSA and ADT. There was significant relation between PSA and orchidectomy. There was high significant relation between bone metastasis and PSA level. There was high significant relation between type of bone metastasis and PSA level.

Our results are supported by study of Koo et al [10] as they reported that patients with higher PSA levels showed more bone lesions ($P < 0.001$).

A positive relation between the PSA level and the incidence of BM was found in the study of Singh et al. [8] ($P = 0.005$ with 95% CI of 1.01–1.10). In patients with PSA >100, all had positive bone scan whereas, with PSA ≤10, none had positive BM. However, interestingly, the incidence of positive bone scan was quite high in their study for patients with PSA = 10.1–20 ng/ml (38.46%). The rate of positive bone metastases with lower serum PSA levels in their study is extremely higher than the United States and Canada (8.9%).

Chybowski et al. [11] documented that the PSA level was correlated with the risk of bone metastasis in 521 patients randomly selected. They suggested that the PSA concentration was the best predictor for bone metastases among other clinical and pathological parameters. In their study, only one patienthad bone metastases among 307 with PSA concentration of 20 ng/ml or less, indicating that the negative predictive value was 99.7%.

Lojanapiwat et al. [7] showed the prevalence of prostate cancer to be 35.39% and the positive predictive value in the diagnosis of prostate cancer when the PSA level was higher than 4 ng/mL to be 37.2%, which is a little higher than in a pooled meta-analysis study (25%). The incidence of prostate cancer in patients with serum PSA<4 ng/mL, >4–10 ng/mL, >10–20 ng/mL, >20–50ng/mL, >50–100 ng/mL, and >100 ng/mL was 10.67%, 16.12%, 21.43%, 47.97%, 82.81%, and 98.55%, respectively. The chance of detection of prostate cancer was about 50% when biopsy was performed at a PSA level of more than 20 ng/mL. There was a strong correlation of PSA level with tumor diagnosis, tumor aggressiveness (Gleason score >7), and positive bone metastasis. The average PSA level for biopsy was extraordinarily high (102.45±411.27 ng/mL) in this study, which can be explained by the very high PSA level (5,000 ng/mL) in one patient with bone metastasis. With a cutoff of ≤25%, the detection of cancer is 95%,and the rate of sparing of biopsies is 20%.Although an elevated correlation was found for Gleason score and PSA level, it did not perform well with the cut-off assigned in clinical practice.

Regarding Szot et al. [12] in patients with a Gleason value ≤7 and a PSA value ≤20 ng/ml, the cutoff value for a negative bone scan with aconfidence interval of 0.95 was established at a PSA value below 10 ng/ml ($p<0.01$). Correlations were established betweenPSA value and presence of metastases in bone scan ($r=0.45$, $p=0.05$), the number of metastases ($r=0.66$, $p<0.01$), and their presence in particular body regions.

Kamaleshwaranet al. [13] reported that of the 153 positive cases, 108 (70%) had serum PSA > 100 ng/ml, 42 (28%) had PSA of 20-100 ng/ml and only 3 (2%) had PSA < 20 ng/ml. All the patients with PSA > 100 ng/ml had multiple skeletal metastasis. Of the 117 negative cases, 110 (94%) had a PSA < 20 ng/ml, 5 had between 20 and 100 ng/ml and only 2 (1.8%) had PSA > 100 ng/ml.
In a population-based observational study, a PSA level >50 ng/mL was observed to correlate with extreme-risk patients, who showed a worse response to treatment and survival outcome than other high-risk patients [14]. Therefore, it is conceivable that the high risk population includes a subset of patients who are at an extreme risk for disease progression and mortality.
If the threshold PSA value was increased to values more than 20.0 ng/ml, bone metastasis could not be sufficiently excluded. PSA thresholds to determine the requirement of a BS has been reported in previous studies with a high negative predictive value (NPV) [15].

8. CONCLUSION

In this study, we found that serum MIF levels are elevated in AS patients. MIF appears to have the unique ability to drive inflammation and could play an important role in the pathogenesis of AS.

REFERENCES

[1]. Dere Y, Akarken I and Sahin H. (2018) The role of preoperative PSA level in prostate cancer.Dere Y et al. Int J Adv Med; 5(4): 780-783.
[2]. Huang Y, Li Z, Huang Y, et al. (2018) Value of free/total prostate-specific antigen (f/t PSA) ratios for prostate cancer detection in patients with total serum prostate-specific antigen between 4 and 10ng/mL: A meta-analysis. Medicine; 97: 13(e0249).
[3]. Loeb S, Bjurlin MA, Nicholson J et al. (2014) Overdiagnosis and overtreatment of prostate cancer. EurUrol; 65(6): 1046–1055.
[4]. Obort AS, Ajadi MB, Akinloye O. Prostate-specific antigen: any successor in sight? Rev Urol 2013; 15: 97-107.
[5]. Lojanapiwat B, Anutrakulchai W, Chongruksut W and Udomphot C. Correlation and diagnostic performance of the prostate-specific antigen level with the diagnosis, aggressiveness, and bone metastasis of prostate cancer in clinical practice. Prostate Int 2014; 2(3): 133-139.
[6]. Crawford ED, Bennett CL, Andriole GL, Garnick MB, Petrylak DP. (2013) The utility ofprostate-specific antigen in the management of advanced prostate cancer. BJU Int; 112: 548-560.
[7]. Lojanapiwat B, Anutrakulchai W, Chongruksut W and Udomphot C. (2014) Correlation and diagnostic performance of the prostate-specific antigen level with the diagnosis, aggressiveness, and bone metastasis of prostate cancer in clinical practice. Prostate Int; 2(3): 133-139
[8]. Singh OP, Yogi V, Redhu P, Ghori HU, Pareek A. (2019) Role of serum prostate-specific antigen as predictorfor bone mestastasis in newly diagnosed prostate cancer.J Can Res The; 15: S341.

[9]. Pai, K., Salgaonkar, G. A., Kudva, R., and Hegde, P. (2015) Diagnostic correlation between serum PSA, gleason score and bone scan results in prostatic cancer patients with bone metastasis. British Biomedical Bulletin; 3(1): 1-7.
[10]. Koo, K. C., Park, S. U., Kim, K. H., Rha, K. H., Hong, S. J., Yang, S. C., and Chung, B. H. (2015) Predictors of survival in prostate cancer patients with bone metastasis and extremely high prostate-specific antigen levels. Prostate International; 3(1): 10-15.
[11]. Chybowski FM, Keller JJ, Bergstralh EJ, Oesterling JE. (1991) Predictingradionuclide bone scan findings in patients with newly diagnosed,untreated prostate cancer: Prostate specific antigen is superior toall other clinical parameters. J Urol; 145: 313-8.
[12]. Szot, W., Kostkiewicz, M., Zajac, J., Owoc, A., and Bojar, I. (2014) Prostate cancer in patients from rural and suburban areas-PSA value, Gleason score and presence of metastases in bone scan. Annals of Agricultural and Environmental Medicine; 21(4).
[13]. Kamaleshwaran, K. K., Mittal, B. R., Harisankar, C. N. B., Bhattacharya, A., Singh, S. K., and Mandal, A. K. (2012) Predictive value of serum prostate specific antigen in detecting bone metastasis in prostate cancer patients using bone scintigraphy. Indian Journal of Nuclear Medicine: IJNM: The Official Journal of the Society of Nuclear Medicine, India; 27(2): 81.
[14]. Alexander, A. S., Mydin, A., Jones, S. O., Christie, J., Lim, J. T., Truong, P. T., & Ludgate, C. M. (2011) Extreme-risk prostate adenocarcinoma presenting with prostate-specific antigen (PSA)> 40 ng/ml: prognostic significance of the preradiation PSA nadir. International Journal of Radiation Oncology Biology Physics; 81(5): e713-e719.
[15]. Ishizuka O, Tanabe T, Nakayama T, Kawakami M, Kinebuchi Y, Nishizawa O. (2005) Prostate-specific antigen, Gleason sum and clinical T stage for predicting the need for radionuclide bone scan for prostate cancer patients in Japan. Int J Urol; 12: 728–32.