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CORRELATION BETWEEN PSA LEVEL AND GLEASON SCORE IN NEWLY DIAGNOSED PROSTATE CANCER PATIENTS IN ARAD COUNTY

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ABSTRACT. Prostate carcinoma (PCa) is the second most common type of cancer among men from North America and Europe. Histopathological diagnosis of PCa can be established by transrectal ultrasound-guided (TRUS) biopsy after an abnormal finding in digital rectal examination or finding an increased value of prostate specific antigen (PSA) in the blood. The purpose of this study is to evaluate the correlation between PSA level and Gleason score, in order to predict prostate cancer aggressiveness at time of diagnosis.
KEY WORDS: prostate, cancer, PSA, Gleason, score.

INTRODUCTION

Prostate carcinoma (PCa) is the second most common type of cancer, as well as the second most common cause of cancer-related death among men from North America and Europe [1,2]. This disease is a serious health concern, especially in developed countries where the elderly population is growing [3]. Histopathological diagnosis of PCa can be established by transrectal ultrasound (TRUS) prostate biopsy, after an abnormal finding in digital rectal examination (DRE) or finding an increased value of prostate specific antigen (PSA) in the blood [3]. An elevated PSA level is not specific only for PCa, but it can also be associated with other prostate pathologies such as benign prostate hyperplasia (BPH) or prostatitis.[3] Despite this disadvantage, PSA measurement remains the gold standard in clinical practice, given that no new biomarkers are currently accepted for diagnosis of prostate cancer. The purpose of this study is to evaluate the correlation between PSA level and Gleason score, in order to predict prostate cancer aggressiveness at diagnosis.

MATERIAL AND METHODS

This was a prospective study which took place between October 2015 and September 2017. The study included 59 patients who signed the informed consent, with the following inclusion criteria: abnormal DRE and PSA level (> 4 ng/dl), who underwent TRUS prostate biopsy. After PCa detection through histopatological examination, the patients were divided into 3 groups according to cancer agressivness, in terms of mild (< 7), moderate (= 7), and high (>7) Gleason score. The patients were also classified according to PSA levels, in two groups: PSA 4-10 ng/ml and PSA > 10ng/ml. This division was made in order to highlight patients diagnosed with PCa who belong in the ‚grey zone'(4-10ng/ml).

Furthermore, the groups were compared to each other accordin to age, PSA level and Gleason score.

STATISTICAL ANALYSIS

All statistical analyses were conducted using Statistica version 7 (StatSoft Inc., Tulsa, USA). In all cases, a p value < 0.05 was considered significant. Based on the Gleason score, the men were stratified as having low-risk PCa (Gleason score < 7), moderate-risk PCa (Gleason score = 7), and high-risk PCa (total Gleason score > 7), respectively. The inter-group homogeneity of age among different groups was checked with a Median test. The blood PSA levels across different classes of PCa were compared using a Median test, with Mann-Whitney tests against the low-risk PCa group being conducted in the case of significant differences. Finally, we investigated the relationship between PSA and PCa aggressiveness using Spearman's rank correlations.

RESULTS

Prostate cancer can be an evasive diagnostic, because of the wide heterogenity refering to age, PSA level and Gleason score. A positive biopsy result was found in all patients. The PSA level corresponded well with the diagnosis of prostate cancer. All recorded patients showed a PSA level above 4ng/ml, the majority of patients had a PSA level above 10 ng/ml (88%), the rest of patients (12%) belonged in the „grey zone" (4-10 ng/ml).

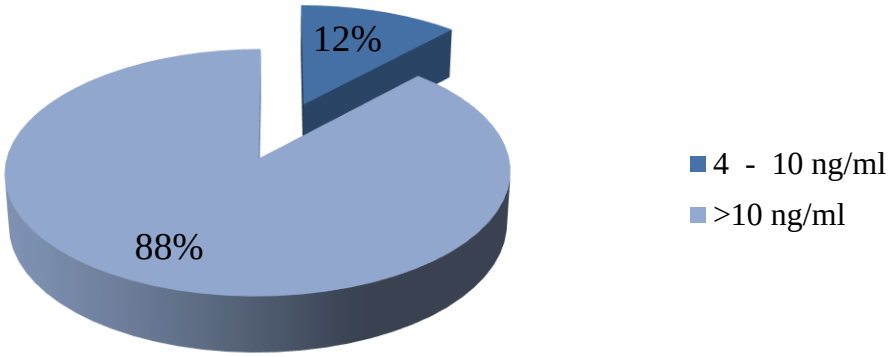
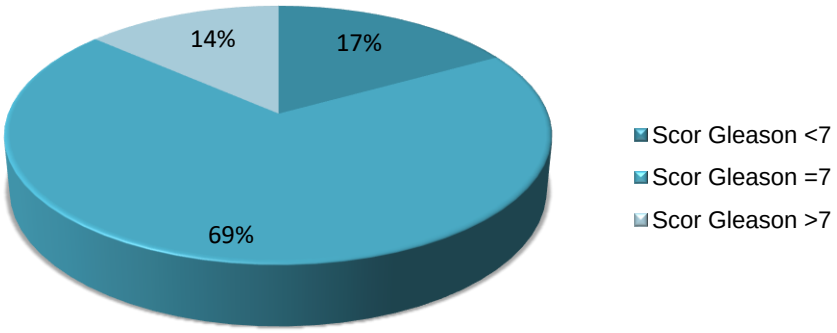


Fig. 1. Partition of PCa patients acording to PSA level

The majority of subjects who participated at this study had the age between 60 and 79 years (49 subjects, 83%), with a median age of 68,9 years, and a PSA level >10 ng/ml.

The Gleason system is used to clasify prostate cancer agressivness. Based on the Gleason score, the men were stratified as having low-risk PCa (Gleason score < 7), moderate-risk PCa (Gleason score = 7), and high-risk PCa (total Gleason score > 7), respectively. [4]

Fig. 2. Distribution of PCa patients according to Gleason score



According to prostate cancer aggressiveness, 14% of subjects had high grade PCa, the majority of subjects (69%) were recorded with intermediate grade of PCa and 17% of patients had low grade PCa. Medium level Gleason score = 7 is considered ambigous because of Gleason Sum variability (7=3+4, 7=4+3). Pattern 4 plays a key role in differentiating cancer agressivness, as cancerous tissues with pattern 4 > 50%, are much closer to evolve like an high risk cancer. (7) Our study shows that 56% of patients had Gleason sum (3+4) the rest of 44% were recorded with a Gleason sum (4+3).

Table1. Distribution of subjects according to Gleason score

Gleason score	Nr. Cases
Score Gleason 4 (2+2)	2
Score Gleason 5 (2+3)	6
Score Gleason 6 (3+3)	2
Score Gleason 7 (4+3)	18
Score Gleason 7 (3+4)	23
Score Gleason 8(3+5)	2
Score Gleason 8(4+4)	3
Score Gleason 9	3

When stratified based on the aggressiveness of PCa, the average age of patients were 68.80 ± 4.98 years for low-risk PCa patients; 69.65 ± 7.09 years for medium-risk PCa patients; and 65.37 ± 6.88 years for high-risk PCa patients. The measured values were homoscedastic (*Levene's* test, $p = 0.604$) and similar among different classes of PCa aggressiveness (ANOVA, $p = 0.257$), thus attesting to the homogeneity of groups in terms of patient age.

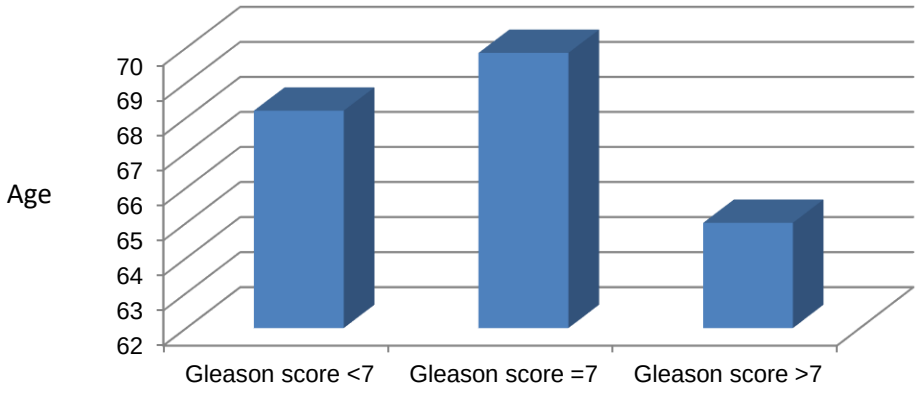


Fig.3. Median age values according to Gleason score

The highest number of patients with aggressive PCa, developed the disease earlier compared to the rest of the groups. Inspite the lack of statistical power due to the small cohort of patients, this was not a surprize for us, because Arad county is considered a hot spot for cancer, due to high concentrations of arsenic found in drinking water from ground water. [5]

Table 2. Measured values of blood *PSA* levels in PCa patients with different Gleason scores

Gleason score	Sample size	Blood PSA level		
		Median	Q25	Q75
4 (2+2)	2	34.36	8.72	60.00
5 (2+3)	6	18.95	16.00	30.27
6 (3+3)	2	44.00	28.00	60.00
7 (3+4)	23	34.00	11.21	224.00
7 (4+3)	18	31.70	18.00	169.00
8 (3+5)	2	521.50	43.00	1000.00
8 (4+4)	3	93.37	39.00	110.00
9 (4+5)	3	109.00	99.17	300.00

Data are shown as medians with lower quartiles (Q25) and upper quartiles (Q75).

Among the patients investigated, 10 patients had low-risk PCa (16.94%), 41 had medium-risk PCa (69.49%), and 8 patients had high-risk PCa (13.57%). Figure 4 shows the median values (with Q25 and Q75 values) for blood PSA for patients belonging to different classes of PCa aggressiveness. The measured values were significantly different among the groups investigated (*Median* test, $p = 0.006$). When compared with the subjects with low-risk PCa, posthoc comparisons revealed no significant differences in serum PSA for the men with medium-risk PCa (*Mann-Whitney* test, $p = 0.418$), but significantly higher median levels for men with high-risk PCa (*Mann-Whitney* test, $p = 0.006$). We also note a much higher variability of serum PSA for medium-risk PCa and high-risk PCa relative to low-risk PCa.

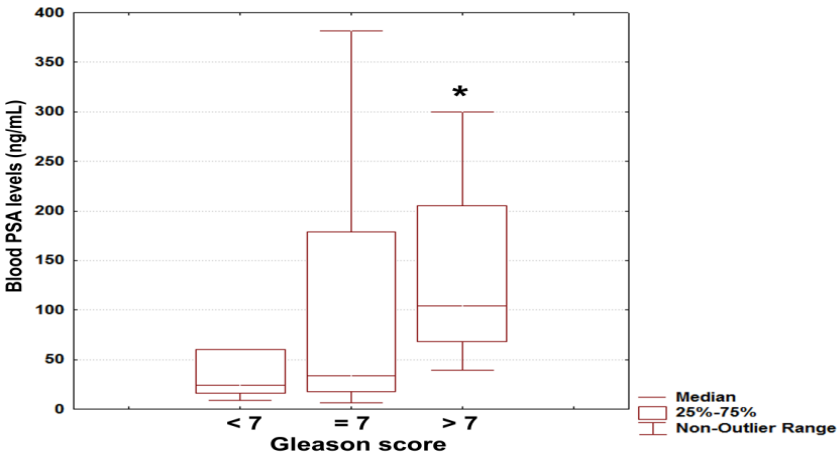


Fig. 4. PSA levels according to different classes of PCa aggressiveness.

Data are shown as medians with Q25 and Q75 values. Marked columns (*) denote significant differences as compared to the low-risk PCa patients (Mann-Whitney test, $p \leq 0.05$).

Our results showed a moderate and significant positive association between PCa agresiviness and PSa levels in the blood ($r_s = 0.28$, $p = 0.027$). This suggest an overall trend towards increasing blood PSA levels with the PCa aggressiveness.

DISSCUSION

Selection of patients was made by PSA cut off value of 4ng/ml, a positive biopsy result was found in all patients. The PSA level corresponded well with the diagnosis of prostate cancer. All 59 patients who participated at the study had a PSA value above 4 ng/ml, the majority of them (88%) had a PSA above 10 ng/ml.

Despite that the PSA cut off value of 4 ng/ml remains the gold standard of screenig and early detection of prostate cancer, studies atest Pca cases with a PSA under 4 ng/ml. This fact leaded to lowering of PSA cut off value, which resulted with elevated number of false negative biopsy punctures. PSA remaines an organ specific biomarker and can present elvated values also in benign entities, like BPH or cronic inflamatory diseases. [6]

A study made by Partin, revealed that correlation exists between PSA and patologic clinical stage of prostate cancer: 80% of subjects with a PSA < 4 ng/ml have an organ localised disease, over 50% of patients with a PSA > 10 ng/ml have extracapsulary disease, and 75% of patients with a PSA > 50 ng/ml have positive pelvic limph nodes. [7]

Also world wide screening programs defined the interval of PSA value between 4-10 ng/ml, as the „grey zone", in order to make a carefull distinction between BPH and PCa, reduceing this way the number of false negative biopsies. When dealing with „grey zone" values, the use of complemantary biomarkers is needed, like Free PSA or PCA 3. [8]

All subjects who participted at the study had the age over 50 years, with a median of 68,9 years, the majority of them (49subjects, 83%), had the age between 60 and 79 years old. This result is in acquaintance with the scicentific literature in terms that the majority of patients affected by prostate cancer are over 50 years old, most of them have between 65 and 69 years. [9]

Oesterling et al, proposed using age intervals in order to enhance early prostate cancer detection and to elarge the specificity of PSA at elderly patients, because PSA cutoff values < 4ng/ml do not reflect prostate volume changes related to age in development of BPH. Oesterling et al, reported a general specificity of 95/%, within the following age intervals:

- Age: 40-49 years-0-2,5 ng / ml;
- Age: 50-59 years -0-3,5 ng / ml;
- Age: 60-69 years -0-4,5 ng / ml;
- Age: 70-79 years -0-6,5 ng / ml.

Using these age references in clinical practice, has lead to early diagnosis of prostate cancer with potential radical cure, in men under 60 years old, also to the increase of diagnosing insignificant (low grade) prostate cancer, which resulted in over treatment of this disease. If the purpose of using the age intervals is to identify the bigest number of prostate cancers, then all aged males should be tested. [6,12]

Our study revealed that indifferent of ages status the mjority of patients had a PSA >10 ng/ml, 44% belonged in the age group 60-69-years. Acording to age intervals, all patients included in the study had higher age references then Oesterling et al reported.

Gleason sistem is used to clasify prostate cancer agressivness. Based on the Gleason score, the men were stratified as having low-risk PCa (Gleason score < 7), moderate-risk PCa (Gleason score = 7), and high-risk PCa (total Gleason score > 7), respectively.

According to prostate cancer aggressiveness, 14% of subjects had high-risk PCa, the majority of subjects (69%) were recorded with intermediate-risk of PCa and 17% of patients had low-risk PCa.

Subjectcs with Gleason score 7 were divided in terms of cancer agressivness, according to Gleason sum of patterns, 7=3+4 and 7=4+3. Stamey showed that pattern 4 plays a key role in differentiating cancer agressivness, as cancerous tissues with domminant pattern 4 > 50%, are much closer to evolve like an high risk cancer. [7]

Our study revealed that *56%* of patients had Gleason sum 7 (3+4) the rest of 44% were recorded with a Gleason sum 7(4+3).

Scientific literature published by Pietro Pepe and Michele Pennisi attests that Gleason score increases with the age of patients and they demonstrated a significant correlation between Gleason score ≥ 8 and elderly men over 80 years old. [9,13]

When discussing age values according to Gleason score, the highest number of patients with aggressive PCa, had a median age of 65.37 ± 6.88 years. This sugests an early debut of agressive disease , compared to the rest of groups and it could be related to the fact that Arad county is considered a hot spot for cancer, due to high concentrations of arsenic found in drinking water from ground water. [5] This observation is in contradiciton with scientific literature.

Prostate gland develops with age, and every gram of tissue determins an increase of total PSA s. Adenomatos tissue determins an increase of PSA with 0,3 ng/ml and cancerous tissue with 3,5 ng/ml. [10]

Most of PSA quantity is produced in the tranzition zone, where prostate adenoma develops, a relatively small quantity of PSA is produced in the periferic zone of prostate where 80% of cancers develop. Types of cancer wich develop from tranzition zone, tend to produce big amounts of PSA. [11]

Prostatic cancerous cells with higher grade of agressivness, tend to lose their capacity to produce PSA. Prostate cancer with Gleason score 9 produces less PSA then one with Gleason score 6, and some patients with advance stage of disease can have low levels of PSA. [7,14]

In our study, subjects with Gleason 8 score, had the highest median PSA value of 257 ng/ml, where as the smallest median PSA value – 44ng/ml, was identified at patients with Gleason 6 score. Our results showed a moderate and significant positive association between PCa agresiviness and PSa levels in the blood (r_s = 0.28, p = 0.027).

CONCLUSIONS

A positive biopsy result was found in all patients.

The PSA level corresponded well with the diagnosis of prostate cancer.

All patients had a PSA value above 4 ng/ml, the majority of them, had a PSA above 10 ng/ml.

All patients included in the study, had higher age references then recorded age intervals used in guidelines.

The majority of subjects were recorded with intermediate PCa risk.

The dominant number of patients with high risk PCa developed the disease earlier compared to the rest of groups, with medium and low risk PCa.

According to our study, there is a relationship between PSA level and Gleason score at time of diagnosis, which suggests an overall trend towards increasing blood PSA levels with the PCa aggressiveness. Therefore, PSA remains a good indicator for predicting the Gleason score.

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