Research Article

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Correlation between the Total Initial PSA , PSA Density, and Prostate Cancer Aggressiveness: A Retrospective Study In Two Urology Centers In Cameroon

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ABSTRACT

Objectives: *Our study aimed to determine the relationship between the initial total prostate-specific antigen (PSA), PSA density, and aggressiveness of prostate cancer (PCa) based on the new Gleason grade group in the two specialized urology centers in Cameroon.*

Method: *A seven-year retrospective study was conducted from January 2012 to December 2019. The study concerned all men diagnosed with PCa graded using the novel Gleason grade group. Data were analyzed descriptively and analytically using Statistical Package for Social Sciences (SPSS) version 20.0. Bivariate analysis was done to identify independent associations.*

Results: *A total of 253 files were reviewed; fulfilling the inclusion criteria. The mean age of our study population was 66.62±8.288 years with the most affected age being those aged between 59-69 years. The commonest finding on DRE was a hard-craggy prostate (46.0%). The mean initial total PSA was 98.78 ng/dL ± 300.17 ng/mL, while the mean PSA density was 1.73 ± 5.94ng/mL². Gleason grade group 2 was the commonest grade (30.6%). There was a positive correlation between initial total PSA and Gleason grade group (r = 0.314 (p-value 0.000)), and between PSA density and Gleason grade group (r = 0.919 (p-value 0.000)). Initial total PSA and the Gleason grade groups were independently associated with the radiological tumour stage (p-value 0.000 and p-value 0.03 respectively).*

Conclusion: *There is a positive correlation between initial total PSA, PSA density, and novel Gleason grade group. We, therefore, recommend that more attention should be placed on PSA density in pre-biopsy decision-making. This study enhances the stratification of therapeutic protocols for the management of PCa in Cameroon as well as across African Union member states.*

Keywords

Prostate cancer, Initial total PSA, PSA Density, Aggressiveness, Cameroon.

Abbreviations & Acronyms

AU = African Union, BMI = Body mass index, CT-Scan = Computerized Tomography Scan, DRE = Digital rectal examination, ENT = Ear Nose and Throat, GS = Gleason Score,

PCa = Prostate Cancer, PSA = Prostate Specific Antigen, SSA = Sub-Saharan Africa, USA = United States of America, WHO = World Health Organization.

Introduction

Globally, prostate cancer (PCa) is the most commonly diagnosed malignancy and the sixth leading cause of cancer death in men [1]. PCa is a heterogeneous disease with a wide spectrum of clinical, pathological, and molecular features [2]. Moreover, PCa is a global public health issue with a prevalence that varies widely across regions and ethnic groups over the world, and as of 2018; there were 1,276,106 new cases of PCa, causing 358,989 deaths (representing 3.8% of all deaths) [3]. Men of African origin/descent are known to have the highest prevalence of PCa due to socio-cultural, economic, and genetic factors, as well as variations in care delivery and treatment selection [4]. Further evidence suggests that relative to other races, PCa mortality rates are typically greater among largely black African communities [5]. Reports show that PCa incidence and mortality rates in Sub-Saharan Africa (SSA) were 34.3 and 22.1 per 100,000, respectively [5]. PCa is the predominant malignant urogenital tumor in Cameroon [6] and represents the 4th histologically diagnosed cancer in Cameroon, with a prevalence of 6.3% [7].

The rising prevalence of PCa has led to the need for developing better screening methods for its diagnosis [3]. Digital rectal examination and Prostate Specific Antigen (PSA) are still the main primary screening tools for PCa in most parts of the world [8]. The normal range of initial total PSA in our setting is <4ng/dL with a slight age-adjusted rise in its value. Though not 100 % specific, PSA has contributed in reducing the rate of undiagnosed cases of prostate cancer [9]. Since 1960, the Gleason score with its nine histologic patterns stratified into five sub-groups has greatly contributed to the improvement of the quality of PCa diagnosis [10]. The Gleason grading system, which has undergone several modifications, is a PCa grading system that is based on the appearance of the cancer cells and their likelihood to spread and advance [11,12]. A study conducted in Cameroon by Elame et al. [14] depicted a correlation between PSA and the aggressiveness of PCa using the old Gleason score. However, to ascertain the relationship between the Gleason score and PSA, studies [15,16] have been conducted; leading to the implementation of the New Gleason Grade. Several studies have been carried out all over the world to elucidate the relationship between PSA, PSA density, and the new Gleason Grade Group, but there is limited data in Cameroon, thus, prompting the public health importance of this study. Since the approval of the new Gleason grade group in 2014, many countries have instituted its use because of its relatively higher index of suspicion for more aggressive prostate cancers. Cameroon still uses the old Gleason classification system for the grading of prostate cancer, hence the need for this study to establish the relationship between the initial total PSA, PSA density, and aggressiveness of PCa based on the new Gleason grade group.

Methods

Study Design, Setting, and Participants

This study was a seven-year retrospective descriptive and analytical study, involving confirmed PCa cases. The cases under study were patients with PCa diagnosed in an approved pathology unit after an 8-12 core sextant ultrasound-guided prostate biopsy and graded using the new Gleason grading system. The retrospective data were collected from the medical reports using a pre-tested data extraction form.

This study was carried out at the Urology unit of the Limbe Regional Hospital, South West region of Cameroon, and at the Medico Surgical Center of Urology, Douala, Littoral region of Cameroon.

All cases diagnosed with PCa from January 2012 to December 2019 at the two Urology Services in Cameroon were considered such that all records were purposefully sampled to confirm the diagnosis of PCa, graded using the new Gleason grading system.

Study Procedure

Administrative clearance for this study was obtained from the Regional Delegation of Public Health for the Southwest region and the Littoral region of Cameroon. Ethical approval was granted by the Institutional Review Board of the Faculty of Health Sciences, University of Buea, Cameroon. Participants' confidentiality was respected by not collecting patient's names nor identity card numbers and the data collected from hospital records was kept and used only for research purposes.

Data Collection, Management, and Analysis

A pre-tested data extraction form was used to collect the desired data. Each form was coded and collected the following information: (i). Socio-demographic characteristics such as age; sex; profession; residence, family history of PCa and other cancers, (ii). Signs and Symptoms of prostate cancer; and Digital Rectal Exam (DRE) findings, (iii). Para-clinical investigations including Biopsy results and (iv). Treatment and outcome.

Extracted data were recorded into Microsoft Excel version 2016 and analysed using Statistical Package for Social Sciences (SPSS) software, version 20.0 [17]. Continuous variables were presented as means (standard deviation) when the distribution was symmetrical or median when skewed. Categorical variables were expressed as percentages. Correlations and associations were computed using the chi-squared test. The independent variables included age, family history, initial PSA, and PSA density while the dependent variables were PCa aggressiveness, Gleason score, and radiological tumor stage. The elements of the descriptive statistics made it possible to calculate frequencies and proportions. The threshold for significance was set at a p-value <0.05.

Results

Participants enrolment

We had a total of 420 files with prostate cancer, 47 files were excluded due to incomplete data, and 120 were excluded because they had a Gleason score of less than 6. A total of 253 files were included in data analysis (Figure 1).

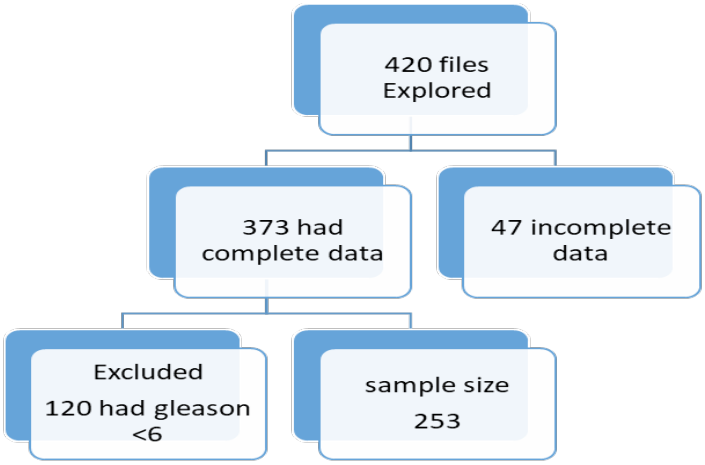

Figure 1: Flow Chart of participant enrolment in two Urology Services in Cameroon.

Characteristics of the study population

The ages of the 253 patients ranged from 45-89 years with an average of 66.62 ± 8.288 years. Teachers (59:23.3%) and farmers (49: 19.4%) were the most affected groups. Also, of the 253 total participants, 77 (43.75%) participants were found to be hypertensive, 35 (13.83%) were diabetic, and 18 (7.11%) had smoked. Data from 98 participants enabled us to compute the body mass index (BMI). A total of 58 (59.2%) participants had BMI >25kg/m². A positive family history of PCa was found in 8 (3.16%) patients and 3 (1.19%) patients had a family history of other cancers.

Clinical presentation

Most patients presented with more than one symptom. The most frequent reason for a urologic consultation was an increase in the initial total PSA accounting for 160 (42.8%) patients, while the commonest presenting symptom was obstructive lower urinary tract symptoms (35.8%) (Figure 2).

Digital rectal examination (DRE) findings

The most common finding on DRE was a hard craggy prostate seen in 116 (46.0%) patients. Of the 253 patients, 31 (12.3%) had a normal prostate on DRE (Table 1).

Table 1: DRE Findings in two Urology Services in Cameroon.

Variables	Class size	Proportion (%)
Hard/craggy irregular prostate	116	46.0
Nodular prostate	45	17.9
Enlarged prostate	14	5.2
Normal prostate	31	12.3

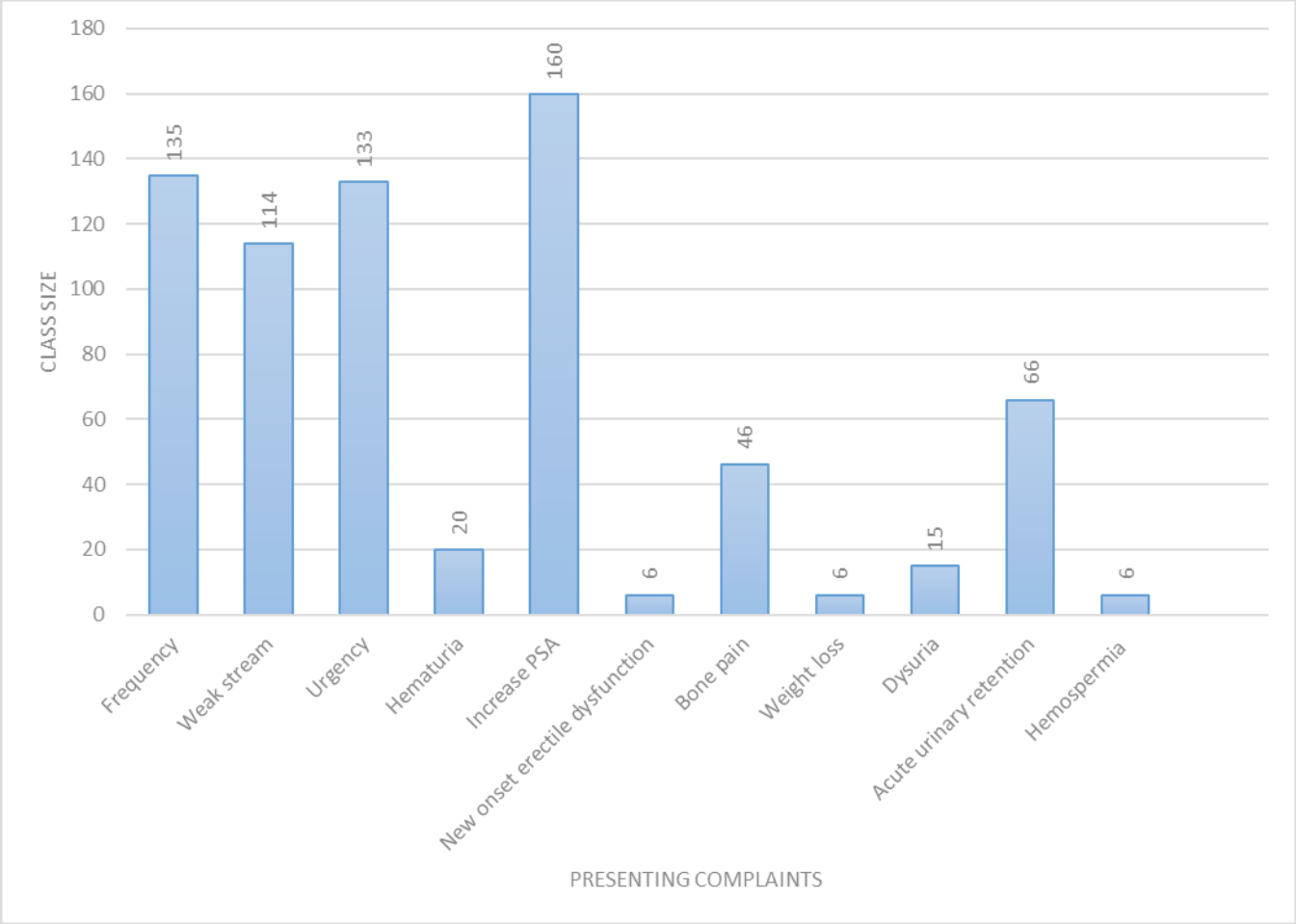

Figure 2: Distribution of patients according to clinical presentation in two Urology Services in Cameroon.

Initial total PSA Distribution

The mean PSA was 98.78 ± 300.17ng/mL. More than half, 147 (58.3%) of the patients had PSA ranging between 10 and 49.9 ng/ml. A PSA level of at least 50 ng/mL was recorded in 73 (28.6%) patients (Table 2).

Table 2: Initial Total PSA Distribution in two Urology Services in Cameroon.

PSA RANGES (ng/mL)	Class size	Proportion (%)
<4.0	1	0.4
4-9.99	32	12.7
10-49.99	147	58.3
≥50	73	28.6
Total	253	100
Mean PSA:	**98.78 ± 300.17ng/mL**	

PSA Density Distribution

More than half, 101 (60.1%) of the patients had PSA density ranging from 0.15 to 0.99 ng/mL². Only, 4.8% of the participants had a PSA density of at least 5 ng/mL² (Table 3).

Table 3: PSA Density in two Urology Services in Cameroon.

PSA DENSITY RANGES (ng/mL²)	Class size	Proportion (%)
<0.15	14	8.3
0.15-0.99	101	60.1
1-4.99	45	26.8
≥5	8	4.8
Total	**168**	**100**

The Novel Gleason grade group of the study population

In this study, the Gleason grade of group 2 occupied the highest position, 77 (30.6%) patients, followed by those in group 1, 59 (23.4%) patients, as seen in Table 4.

Table 4: Novel Gleason Grade group in two Urology Services in Cameroon.

Variables	Class size	Proportion (%)
Group 1 (Gleason 6)	59	23.4
Group 2 (Gleason 3+4)	77	30.6
Group 3 (Gleason 4+3)	32	12.7
Group 4 (Gleason 4+4)	48	19.0
Group 5 (Gleason 9 or 10)	37	14.3
Total	**253**	**100**

Relationship between Initial total PSA and Gleason grade group

A majority, 58 (75.3%) of the patients within a PSA range of 10-49.99 ng/ml were in Gleason grade group 2. There was a significant association between initial total PSA and Gleason grading (p=0.000) as seen in Table 5**.**

Table 5: Association between PSA and Gleason grade group in two Urology Services in Cameroon.

Variable	Gleason grading groups					
PSA RANGES (ng/mL)	**Group 1**	**Group 2**	**Group3**	**Group 4**	**Group 5**	**P value**
<4.0	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	**0.000**
4-9.99	8 (13.6)	17 (22.1)	7 (21.9)	0 (0.0)	0 (0.0)	
10-49.99	34 (57.6)	58 (75.3)	22 (68.8)	31 (64.6)	2 (5.6)	
≥50	17 (28.8)	1 (1.3)	3 (9.4)	17 (35.4)	34 (94.4)	

Correlation between Initial total PSA and Gleason grade group

Pearson's product-moment correlation index obtained on initial total PSA and overall Gleason score was r = 0.314. It shows a significant moderate positive (p-value = 0.000) correlation between initial total PSA and overall Gleason score as seen in Figure 3.

Association between Gleason grade group and radiological tumor stage

There was an association between the Gleason grade group and the tumor stage (p 0.03). Tumour stage 2 was commonest among patients with Gleason grade group 1 (51.8%), Gleason grade group 2 (41.4%), and Gleason grade group 3 (50.0%), while stage 4 was commonest among Gleason grade group 4 (59.5%) and Gleason grade group 5 (55.9%) as seen in Table 6.

Table 6: Gleason Grade groups and radiological tumor stage cross-tabulation in two Urology Services in Cameroon.

	S1	S2	S3	S4	TOTAL
G1	9	29	1	16	55
G1	9	29	1	16	55
G2	12	24	1	21	58
G3	3	13	1	9	26
G4	6	8	1	22	37
G5	0	14	1	19	34
Total	30	88	5	87	210
P value	**0.03**				

Association between PSA density and Gleason grade groups

The majority, 21 (84.0%) of the patients within a PSA density between 0.15 and 0.99 ng/ml² were in Gleason grade group 3. There was a significant association between PSA and the Gleason grade groups (p=0.000) (Table 7).

Table 7: Association between PSA density and Gleason grade group in two Urology Services in Cameroon.

Variable	Gleason grading groups				
PSA DENSITY (ng/ml²)	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**P value**
<0.15	10 (16.9)	4 (16.0)	0 (0.0)	0 (0.0)	**0.000**
0.15-0.99	49 (83.1)	21 (84.0)	31 (64.6)	0 (0.0)	
1-4.99	0 (0.0)	0 (0.0)	17 (35.4)	28 (77.8)	
≥5	0 (0.0)	0 (0.0)	0 (0.0)	8 (22.2)	

Correlation between PSA density and Gleason grade groups

Pearson's product-moment correlation index obtained on PSA density and Overall Gleason score was r = 0.919, showing a significant (p-value = 0.000) strong positive correlation between PSA density and overall Gleason score (Figure 4).

Discussion

Our study which aimed at relating initial total PSA and PSA density to the aggressiveness of PCa based on the new Gleason score showed that the initial total PSA and PSA density correlated to the aggressiveness of PCa based on the Gleason score. This study is among the very few others in Cameroon addressing the association of initial total PSA and PSA density to the aggressiveness of PCa based on the novel Gleason score. Although the mortality rate from

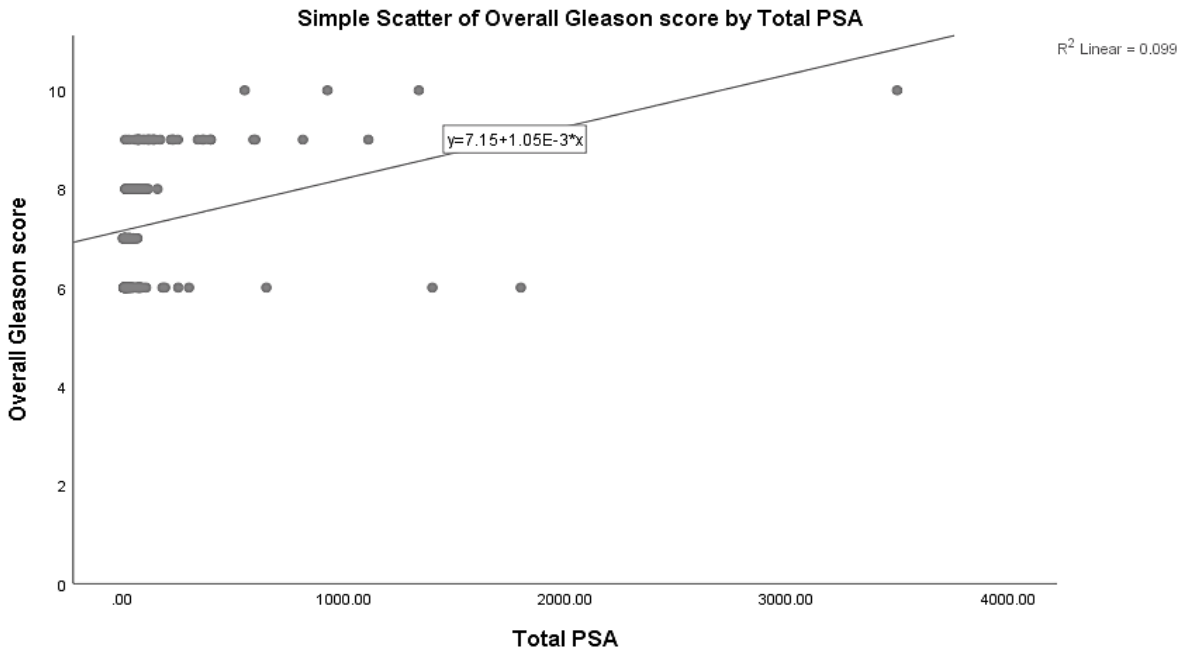

Figure 3: Correlation between Initial total PSA and Gleason Grade groups in two Urology Services in Cameroon.

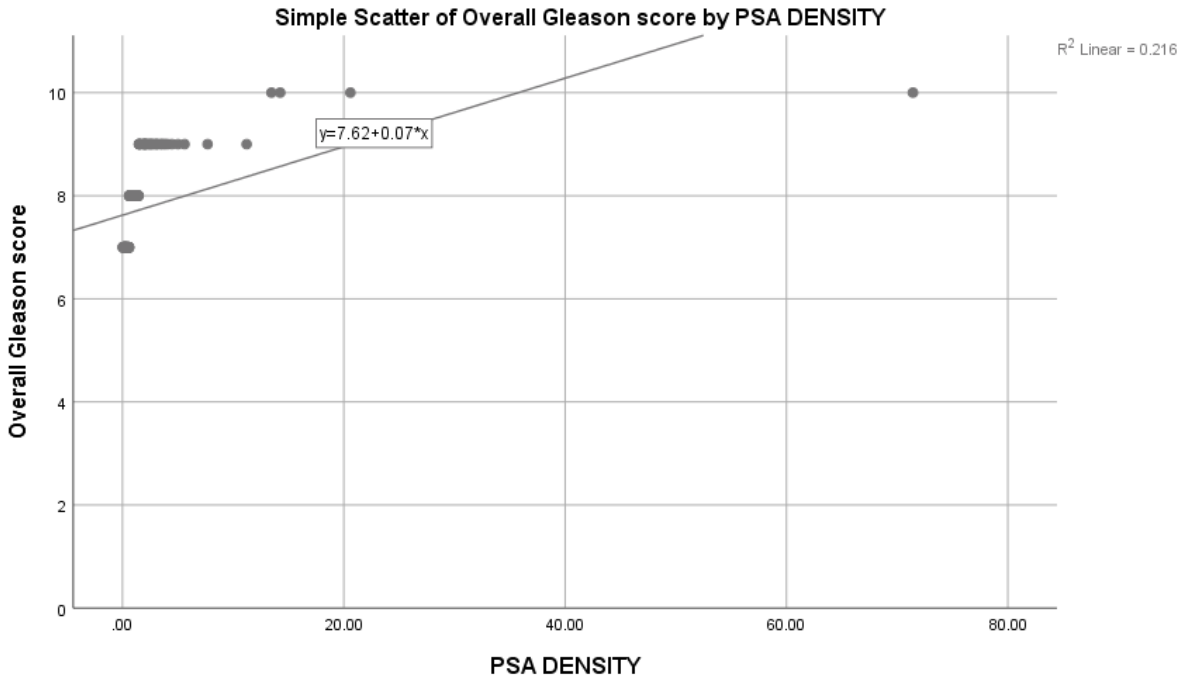

Figure 4: Correlation between PSA Density and overall Gleason grade score in two Urology Services in Cameroon.

the disease was greatly decreased, the number of new instances of PCa dramatically increased with the introduction of PSA-based screening in the early 1990s [18]. In a randomized European Study, it was shown that there is a great disparity between the incidence and the mortality of PCa [19]. PSA and DRE remain the universally accepted screening tools for prostate cancer [20], while the Gleason score remains the commonest grading system for prostate biopsy samples including in resource-limited settings [21].

Previous studies have demonstrated that PCa incidence increases with age, [22,23] even though a study by Kamadjou et al. [24] conducted at the medico-surgical center of urology in Douala showed that familial prostate cancers occurred at early ages and were more aggressive. The mean age in our study is similar to that of Ntemgwa et al. [7] in 2017 in Cameroon where the mean age of their participants was 69 ± 9.2 years, with the most affected age group being those between 70 to 80 years [25]. This similarity in

the age groups may be because in both study populations patients usually presented at a late symptomatic stage with a good number of them at the level of complication (metastasis).

Lower urinary symptoms (35.8%) was the commonest presenting complaint in the present study. This is similar to the finding reported by Tchinda et al. [26] where lower urinary tract symptoms were the main clinical features at presentation. This similarity may be accounted for by the fact that both studies were hospital-based, invovling already diagnosed PCa patients. This result is, however, different from results gotten by Angwafo et al. [27] in 2003, in Cameroon, where 69.96% of participants were asymptomatic. This difference may be accounted for by their small sample size.
In the present study, DRE was systematically conducted for all participants after measurements of PSA titers. The commonest finding was a hard craggy prostate (46.0%), while 17.9% presented with a nodular prostate. These results are different from those found by Angwafo et al. [27] where 33 (34.74%) participants had enlarged glands with benign consistency. The difference may be due to the fact that our study was a hospital-based study where all our participants were already diagnosed with prostate cancer.

The mean initial total PSA in our study was 98.78± 300.17 ng/dl. Our results are closer to those of Nnabugwu et al. [28] in Nigeria, who had a mean initial PSA of 46.7 ± 61.3ng/dL. These results are, however, different from those found by Bunker et al. [29] in the Island of Tobago and Kotb et al. [30] in Canada, where they found a mean initial total PSA of 14.8 ± 376ng/dL and 5.9ng/mL respectively. The lower mean in their study could be accounted for by the fact that Bunker et al. included both patients with and without confirmed PCa in a population-based study, while Kotb et al. included patients who mainly had gland-confined tumors. In our study, most patients presented with tumors having distant metastasis [31].

In the present study, the most common Gleason grade group was Gleason grade group 2, accounting for 77 (30.6%) patients. This is similar to the results found by Grober et al. [32] where grade group 2 was the commonest grade, accounting for 72.2%, probably because both studies had comparative sample sizes and near-to-similar inclusion criteria.

Our study established a positive correlation between the initial total PSA and the Gleason grade group with a Pearson correlation coefficient of r = 0.314 (p=0.000). Our results are similar to those obtained by Lojanapiwat et al. [33] in 2014 and Okolo et al. [34] in 2008. These two studies had similar sample sizes to ours, used ultrasound-guided biopsy, and employed the new Gleason grading system as was the case in our study. However, Nabugwu et al. [28] from Nigeria did not find any correlation between the initial total PSA and the Gleason grade group as they used digitally guided sextants biopsy [35] as opposed to the ultrasound-guided prostate biopsy used in the current study.
We found a strong association between initial total PSA and radiological tumor stage, similar to the findings of Leapman et al. [36] in 2016, the in the United States, where patients with higher initial total PSA titers had more distant metastasis as compared to those with lower initial total PSA titers. As was the case in our study, their study involved black Africans who are reported to have genetically more assaultive tumours [37]. Furthermore, we found an association between the novel Gleason grade group and the radiological tumor stage. This is similar to the results found by Leapman et al. [36] who used a similar imaging modality for staging.

In the present study, there was a strong correlation between PSA density and the novel Gleason grade groups (Pearson correlation coefficient, r=919 (p = 0.000)). This correlation was stronger than that between the initial total PSA and the novel Gleason grade groups. These results are similar to those gotten by Hassanipour et al. [38] in 2016, who also used the novel Gleason grade groups in predicting PCa aggressiveness. On the other hand, Luyan et al. in 2000, did not see PSA density as a predictor of PCa aggressiveness [39].

This study is limited by its retrospective nature. In addition, bearing in mind that, although slide reading for the Gleason grading is a subjective act, we assumed that all patients included in this study were subjected to a fairly standard Gleason grading and scoring.

Conclusion

At the end of this study which was aimed at assessing the relation between Initial total PSA and aggressiveness of prostate cancer, we found a correlation and an association between Initial total PSA and Gleason grade groups. We also found associations between initial total PSA and the extent of disease progression after staging. Likewise, the Gleason grade group was associated with the tumor stage. To the best of our knowledge, this is one of the few studies establishing a relationship between initial total PSA, PSA Density, and aggressiveness of PCa using the novel Gleason grade group in Cameroon. The study was done in urology centers where the majority of urological disorders in Cameroon are referred to for management, which makes us an approximate picture of the disease in Cameroon. The results of this study serves as a pool of knowledge for raising awareness on the attitude to adopt when faced with a patient having a high initial total PSA. This, we hope, will reduce the rate of negative biopsies and enhance decision-making for the next step of the management ladder which is usually delayed in Cameroon and across other African Union (AU) member states.

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