EAS Journal of Biotechnology and Genetics
Abbreviated Key Title: EAS J Biotechnol Genet
ISSN: 2663-189X (Print) & ISSN: 2663-7286 (Online)
Published By East African Scholars Publisher, Kenya

OPEN ACCESS

Volume-5 | Issue-4 | Sep-Oct-2023 | DOI: 10.36349/easjbg.2023.v05i04.002

Original Research Article

Diagnostic Performance of the Free to Total PSA Ratio in the Detection of Prostate Cancer in Patients Over 50 Years of Age at the Brazzaville Hospital Center, Congo

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Article History
Received: 01.08.2023
Accepted: 07.09.2023
Published: 13.09.2023

Journal homepage:
https://www.easpublisher.com

Quick Response Code

Abstract: ***Objective:*** To evaluate the diagnostic performance of total PSA, free PSA and the ratio of free to total PSA in identifying prostate cancer. ***Patients and methods:*** This was a descriptive, cross-sectional study from March 2019 to November 2021. Blood samples were analysed by sandwich ELISA and the ratio of free to total PSA (f/tPSA) was calculated. Prostate biopsies underwent histological analysis and the WHO 2012 Gleason Differentiation Score grading system was used. ***Results:*** 54 patients were selected; after histological examination 26 (48.15%) had prostate cancer (PCa) and 28 (51.85%) had Benign Prostatic Hyperplasia (BPH) (P<0.001). The mean total PSA (tPSA) of patients with PCa (26.1 ± 32.8 ng/ml) was higher than that of patients with BPH (9.64 ± 6.72 ng/ml) (p=0.019). The mean f/tPSA ratio of patients with PCa (14.3 ± 16.3%) was significantly lower than those with BPH (21.8 ± 19.3%). Gleason score was poorly differentiated in patients with tPSA < 4ng/ml and > 10ng/ml in 11.5% and 26.9% respectively. 61.5% of patients with f/tPSA <15% had SG≤6, SG=7 and SG ≥8 in 12.5%, 37.5% and 50.0% respectively. AUC/ROC was significantly higher for f/tPSA ratio (AUC, 0.67; 95% CI, 0.52 to 0.81) than for tPSA (AUC, 0.62; 95% CI, 0.46 to 0.77) and fPSA (AUC, 0.49; 95% CI, 0.34 to 0.65). ***Conclusion:*** Early diagnosis of prostate cancer requires the contribution of different PSA derivatives and the use of cut-off values.

Keywords: Diagnostic performance, f/tPSA, Prostate cancer.

INTRODUCTION

Prostate cancer (PCa) is a disease of the elderly and a major public health problem in developed countries [1]. It is the second most common cancer worldwide and the sixth most common cause of death from male cancer, with an estimated 1.1 million new cases in 2012 [2, 3]. It is the most common cancer in men aged over 50. In the Congo in 2003, PCa ranked first among cancers in men aged over 50, with an estimated incidence rate of 4.06 cases per 100,000 inhabitants [4]. Between 2007 and 2017, cancer-related mortality was 76.37%, including 60.35% for prostate cancer [5]. Screening for prostate cancer is mainly based on serum prostate-specific antigen (PSA) levels and digital rectal examination (DRE) [6]. In recent years, the incidence of prostate cancer has risen sharply, with a lower mortality rate in countries with greater resources than in less developed regions of the world. This increase is largely due to the use of PSA as a diagnostic and prognostic tool for prostate cancer, although its low specificity means that its use as a single biomarker has significant limitations, as its production may be related to the volume of benign hypertrophy, tissue inflammation, recent urogenital infection or the concentration of serum and intra-

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glandular androgens [7]. The sensitivity of the PSA assay is being seriously questioned by the scientific community, given that its specificity or positive predictive value is only around 20%, which is the source of false positives leading to unnecessary prostate biopsies, and this low predictive value of PSA means that up to three-quarters of patients with PSA levels in the grey zone between 4 and 10 ng/ml have negative prostate biopsies [6-8].

The main drawback of PSA is therefore its lack of specificity, which leads to unnecessary or repeated prostate biopsies with false-positive results and the diagnosis of indolent PCa, and therefore a high risk of over-diagnosis and over-treatment [3]. Furthermore, a PSA level considered normal does not rule out the presence of CaP, since one study has shown that 15% of subjects with normal PSA levels have prostate cancer that is sometimes advanced and detectable by biopsy [6, 7]. However, almost a third of these cancers detected by PSA are small, localised cancers that are not very aggressive and probably do not need to be treated at this stage. Conversely, the other two-thirds are larger, aggressive tumours with a high risk of progression and death, requiring early curative treatment [6]. In order to preserve the benefits of screening, early detection and reduce these harms, a great deal of progress has been made in the search for other ways of using the PSA test with better performance characteristics through the discovery of promising new blood and urine biomarkers, in particular free PSA (fPSA), the ratio of free PSA to total PSA (f/tPSA), the [2] form of proPSA (p2PSA), the Prostate Health Index (PHI), the PCA3 gene and the immunohistochemical markers P63, p504s. The aim of this study was to evaluate the diagnostic performance of total PSA, free PSA and the ratio of free to total PSA in identifying prostate cancer in patients with normal and abnormal total PSA levels.

PATIENTS AND METHODS

Patients

This was a descriptive, cross-sectional study conducted over a period of 3 years from 1 March 2019 to 30 November 2021 at the Brazzaville University Hospital in the Urology - Andrology Department for sample collection, at the Research Laboratory of the Faculty of Health Sciences in the biochemistry unit for sample storage and serum determination of the various PSA isoforms and at the Edith Lucie Bongo Ondimba General Hospital in Oyo in the histopathology and clinical cytology functional unit for the histological study. Inclusion criteria were: Patients aged 50 years or older, consenting, having undergone a first prostate biopsy and all surgical specimens of prostatic origin. Non-inclusion criteria were: patients with previous prostate biopsy and surgery, family history of prostate cancer, acute or chronic bacterial prostatitis, urinary tract infection and treatment with 5-α reductase inhibitors. This study was approved by the ethics committee of the National Institute for Research in Health Sciences (IRSSA) of Brazzaville.

Methods

Blood samples were taken in a dry tube from the elbow between 7 and 9 am on an empty stomach away from any prostatic manipulation. After collection, the blood samples were placed in plastic bags and transported for centrifugation and storage under the required conditions. The samples were decanted after centrifugation at 3,000 rpm for 5 minutes, aliquoted and stored at -80°C until the day of the assay. Patients also underwent prostate biopsies performed by a urological surgeon according to a standardised institutional saturation scheme, which consisted of at least 12 needle biopsy specimens obtained under transrectal Ultrasound or ultrasound guidance. These were immediately immersed in 10% diluted formalin. The tPSA and fPSA were determined by sandwich enzyme-linked immunosorbent assay using the Pars Biochem tPSA and fPSA ELISA kit and the total f/tPSA ratio was calculated [% Ratio= f(PSA) / t(PSA)]. A standard histological analysis of the prostate biopsies and the prostatic cut-out was carried out following the steps of dehydration, paraffin embedding, microtomy, obtaining white slides and staining with hemalun-Eosin. Histological type was established using the Gleason Differentiation Score grading system according to the World Health Organization 2012. The study variables were: age, absence and/or presence of cancer, tPSA level, fPSA level, f/t PSA ratio, histological type of cancer and Gleason score.

Statistical analysis

Microsoft Excel version 2013 and R version 4.2.1 were used. Nominal and ordinal categorical variables were expressed as headcount and percentage. Quantitative variables were expressed as mean ± standard deviation or median with interquartile range, depending on whether or not the distribution was normal, as assessed by the Shapiro Wilk test. Comparisons of categorical variables were made using the Chi-square test or Fisher's exact test for small numbers (expected number less than 5). Quantitative variables were compared according to the nature of the distribution using the Student's t test or the Mann Whitney test when the variable had two modalities and the one (01) factor Anova test. Receiver operating characteristic (ROC) curves were used to assess the diagnostic performance of the following tests for serum total PSA, free PSA and the ratio of free PSA to total PSA. The cut-off value was defined using the Youden index. All tests were performed at the alpha risk threshold set at 5%.

RESULTS

During the study period, 54 patients were selected. Histological examination revealed 26 cases (48.15%) of Prostate Cancer and 28 cases (51.85%) of Benign Prostatic Hyperplasia (BPH) (P<0.001). The

mean age of patients with PCa and BPH was 70.7 ± 5.67 years and 66.8 ± 4.72 years respectively, with a predominance in the 70 to 79 (61.5%) and 60 to 69 (51.1%) age groups (p=0.009). The mean tPSA level of patients with PCa (26.1 ± 32.8 ng/ml) was higher than that of patients with BPH (9.64 ± 6.72 ng/ml); PCa and BPH were detected in patients with tPSA levels >4 ng/ml and 10-25 ng/ml respectively in 30.8%, 35.7%, 26.9% and 32.1% of cases (p=0.019). 61.5% of PCa patients and 46.4% of BPH patients had an f/tPSA ratio of less than 15% (table 1).

Table 1: Distribution of PCa and BPH according to f/tPSA

f/tPSA(%)	PCa		BPH		Total	
	n	%	n	%	n	%
<15%	16	61.5	13	46.4	29	53.7
15-25%	7	26.9	8	28.6	15	27.8
>25%	3	11.5	7	25.0	10	18.5
Total	26	100	28	100	54	100

PCa: Prostate Cancer; **BPH**: Benign Prostate Hyperplasia; **f/tPSA**: indicates free to total Prostate Specific Antigen ratio.
P-value= 0,129 OR[IC 95%]=0,97 [1,01 ; 0,94]

The mean f/tPSA of PCa patients (14.3 ± 16.3%) was significantly lower than that of BPH patients (21.8 ± 19.3%). The mean Gleason score (GS) was 7.50 ± 0.86 with extremes of 6 and 9. 38.5% of PCa patients had a GS of 7 and 8. The GS was poorly differentiated in patients with tPSA < 4ng/ml, 4-10 ng/ml, and > 10ng/ml in 11.5%, 11.5% and 26.9% respectively. 61.5% of patients who had an f/tPSA ratio <15% had well-differentiated (SG≤6), moderately differentiated (SG=7), and poorly differentiated (SG ≥8) SG in 12.5%, 37.5%, and 50.0% respectively. 38.4% of patients with a ratio f/tPSA >15% had well-differentiated (SG≤6), moderately differentiated (SG=7), and poorly differentiated (SG ≥8) SG in 10.0%, 40.0%, and 50.0% respectively. The receiver operating characteristic (ROC) curve, which measures the area under curve (AUC), was significantly higher for f/tPSA (AUC, 0.67; 95% CI, 0.52 to 0.81) than for tPSA (AUC, 0.62; 95% CI, 0.46 to 0.77) and fPSA (AUC, 0.49; 95% CI, 0.34 to 0.65) (figure 1).

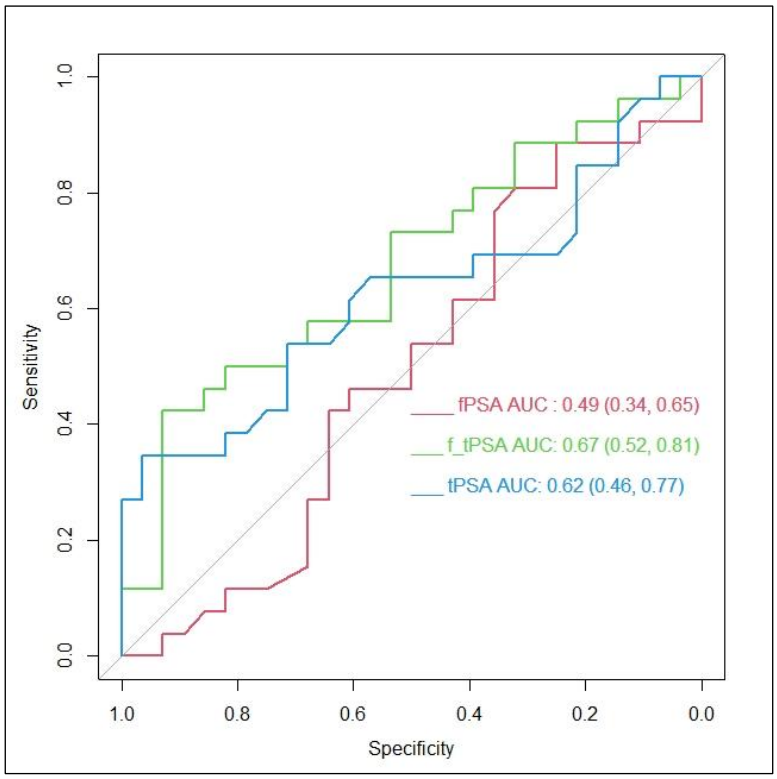

Figure 1: **Distribution of the ROC curves for tPSA range, fPSA, and f/tPSA ratio**
ROC curve of tPSA, fPSA, and f/tPSA ratio. The AUC for the f/tPSA ratio (0.67) was the largest, followed by the tPSA (0.62), and then fPSA (0.49)
ROC: Receiver operating characteristics, **AUC**: area under the curve, **tPSA**: total Prostate Specific Antigen, **fPSA**: free PSA, **f/tPSA**: free to total Prostate Specific Antigen ratio

Using the Youden index (95% CI), the tPSA threshold value was 20.66ng/ml with a sensitivity of 34.6% and a specificity of 96.4%, and at this value 50% of prostate biopsies could be avoided, i.e. 96.4% of BPH patients reported could avoid a prostate biopsy; the f/tPSA threshold value was 81.23 with a sensitivity of 3.8% and a specificity of 96.4%, and at this value 50% of prostate biopsies could also be avoided (table 2).

Table 2: **Assessment of the diagnostic performance of different PSA derivatives**

	AUC	Cut Off Value	Se	Sp	PPV	NPV
tPSA	0.62	20.66	34.6%	96.4%	90.0%	61.3%
fPSA	0.49	53.95	84.6%	32.1%	53.6%	69.2%
f/tPSA	0.67	81.23	3.8%	96.4%	50.0%	51.9%

Youden's index was used at a 95% confidence interval.

AUC: area under the curve, **tPSA**: total Prostate Specific Antigen, **fPSA**: free PSA, **f/tPSA**: free to total Prostate Specific Antigen ratio, **Se**: Sensitivity, **Sp**: Specificity **PPV**: Positive Predictive Value; **NPV:** Negative Predictive Value

In the tPSA range between 4ng and 10ng/ml, the tPSA cut-off value was 7.87ng/ml with a sensitivity of 75.0% and a specificity of 75.0%, and at this value 50.0% of prostate biopsies could be avoided; the f/tPSA cut-off value was 18.0 with a sensitivity of 50.0% and a specificity of 50.0%, and at this value 33.3% of prostate biopsies could be avoided (**table 3**).

Table 3: **Assessment of the diagnostic performance of different PSA derivatives in the PSA range between 4 and 10 ng/ml.**

	AUC	Cut Off Value	Se	Sp	PPV	NPV
tPSA	0.68	7.87	75.0%	75.0%	60.0%	85.7%
fPSA	0.43	144.95	50.0%	62.5%	40.0%	71.4%
f/tPSA	0.63	18.00	50.0%	50.0%	33.3%	66.6%

Youden's index was used at a 95% confidence interval.

AUC: area under the curve, **tPSA**: total Prostate Specific Antigen, **fPSA**: free PSA, **f/tPSA**: free to total Prostate Specific Antigen ratio, **Se**: Sensitivity, **Sp**: Specificity

PPV: Positive Predictive Value; **NPV:** Negative Predictive Value

DISCUSSION

Epidemiological and Socio-Demographic Data

Relative frequency

Prostate cancer is the most common cancer in men over the age of 50. In our study, the relative frequency of PCa and BPH was 48.15% and 51.85% respectively. Our results were similar to those of Pourmand *et al* [9], Simona Ferraro *et al* [10] who reported a frequency of PCa and BPH of 48.5%, 41.5% and 51.5%, 58.5% respectively. Perez-Lanzac *et al* [11] reported a relative frequency of PCa and BPH of 62.02% and 37.97% respectively. This difference may be explained by the fact that the latter study was conducted over a long period with a large population study, which may therefore increase its relative frequency.

Age

Our mean age results are similar to those of Berroukche *et al* [12], Jiahao Shan *et al* [13] who reported mean ages of PCa and BPH patients of 71.63 ± 10 years, 71.13 ± 6.62 years and 68.38 ± 9.40 years, 66.33 ± 7.61 years respectively. LOKO *et al* [14], Xue-Dan *et al* [15] reported a predominance in age groups similar to ours. Most studies have shown that age is closely linked to the onset and development of prostate cancer [13]. Some studies have reported that as age increases, the physiological barrier in the prostate duct is further weakened, increasing the permeability of serum PSA levels. Therefore, it is recommended that different PSA reference ranges should be used at different ages to increase the diagnostic rate of PCa. Age is not only related to serum PSA levels but also correlates with prostate cancer diagnosis and treatment. The age of onset of PCa is mainly concentrated in the middle-aged and elderly population [16-17].

Biological parameters

Total Prostate Specific Antigen

The mean tPSA level of PCa patients (26.1 ± 32.8 ng/ml) was higher than that of BPH patients (9.64 ± 6.72 ng/ml). Pourmand *et al* [9], Berroukche *et al* [12] also reported higher mean tPSA levels in PCa patients than in BPH patients (25.1 ± 23.7 ng/ml, 28.34 ± 63.62 ng/ml and 3.38 ± 1.7 ng/ml, 7.1 ± 10.04 ng/ml respectively). The division of the patients in our analysis into several groups responding to the quantitative presentations of tPSA by bands enabled us to better appreciate the serum distribution of tPSA. PCa and BPH were detected in patients with a tPSA level >4ng/ml and 10-25 ng/ml respectively in 30.8%, 35.7% and 26.9%, 32.1% of cases. The rise in total PSA levels above 20 ng/ml in BPH patients may be transient and due to several factors that disrupt normal PSA production and influence its half-life. Furthermore, circulating serum tPSA concentrations below the threshold value of 4 ng/ml do not guarantee the absence

of prostate cancer [18]. Some authors believe that in some BPH patients, the tPSA value exceeds the threshold value, without knowing the mechanisms of this increase. This fluctuation also applies to patients with prostate cancer who, conversely, may have total PSA concentrations of less than 4 ng/ml [18]. A recent study analysing men with an initial total PSA of less than 4.0 ng/ml who ended up with an elevation of more than 4.0 ng/ml showed that 57% of these total PSA elevations were not related to prostate cancer. Benign prostate disease is a common cause of elevated total PSA levels above 10 ng/ml, which is contrary to the report from Western countries, where prostate cancer is the most common cause of tPSA levels >4ng/ml. This indicates that high or intermediate serum total PSA levels in our patients do not guarantee whether or not a man has prostate cancer [9].

Ratio of free to total PSA

Many studies have shown that f/tPSA is lower in patients with prostate cancer. It is widely accepted that in patients with elevated serum PSA, men with prostate cancer tend to have lower f/tPSA values than men with benign cancer [19]. Our study also supports this, showing that the mean f/tPSA of PCa patients (14.3 ± 16.3%) was significantly lower than the mean f/tPSA of BPH patients (21.8 ± 19.3%). Our results were similar to those of Pourmand et al [9], Zhui-Feng Guo et al [20], Houshang Amirrasouli et al [21], Simona Ferraro et al [10] who reported a mean f/tPSA of PCa patients lower than the mean of BPH patients respectively 13 ± 21%, 15 ± 7%, 12 ± 1%, 16.9 ± 6.8% and 26 ± 24%, 17 ± 6%, 16 ± 3%, 19.2 ± 7.7%. Previous studies have confirmed that a low f/tPSA value predicts a high risk of prostate cancer [22-23]. The f/tPSA ratio was one of the most useful PSA-related markers for suggesting prostate biopsy in patients with intermediate levels of total PSA [24]. The reasons for this difference between patients with BPH and PCa in the molecular forms of PSA are often associated with a more severe form of proteolytic degradation of free PSA as it passes into the extracellular space in benign tissue. The high production of ACT in the intracellular space of the prostate epithelium also leads to an increase in serum PSA-ACT in cancer patients compared with BPH patients [18]. Thus 61.5% of PCa cases and 46.4% of BPH cases had an f/tPSA ratio of less than 15%. The relatively low f/tPSA ratio would indicate that the PSA-ACT fraction is in the majority in BPH. When a threshold f/tPSA ratio of 15% was used as a selection criterion for biopsy, 54% of cancers were detected compared with 33% of non-cancerous cases in normal American men with total PSA levels of 2.51-4 ng/ml [25]. An f/tPSA ratio of less than 15% has been reported by many in the urological literature. Although the number of our patients is not large enough, our results are in agreement with other studies confirming the clinical interest of the f/tPSA ratio in the relative improvement of the specificity of tPSA in the detection of CaP.

Gleason Score, Total PSA and the Ratio of free to total PSA

The mean of GS was 7.50 ± 0.86. Scores Gleason 7 and 8 were the most represented. Our results are consistent with those of Abubakar *et al* [26], who reported a mean GS of 7.15 ± 1.51 and the same representability of the predominance of GS at 7 and 8 was reported by Odubanjo MO *et al* [27], Oluwole OP *et al* [28]. The Gleason score was poorly differentiated in patients with total PSA < 4ng/ml, 4-10 ng/ml, and > 10ng/ml respectively in 11.5% (03), 11.5% (03) and 26.9% (07). Our results are similar to those of Kumari *et al* [29] who reported poorly differentiated GS in patients with tPSA levels between 4-10 ng/ml and >10ng/ml in 01 and 09 cases respectively. Deepika Gurumurthy *et al* [30], Mc Guire BB *et al* [31] reported poorly differentiated GS in patients with a tPSA < 4ng/ml in 5.9% and 17.5% respectively. The results of the various studies on the correlation between Gleason grade and PSA levels before treatment are contradictory. Some studies have reported a positive correlation between the two. According to them, prostate cancer cells produce more PSA than normal cells and, consequently, poorly differentiated cancer cells secrete and release greater quantities of PSA than well-differentiated cells [32, 33]. On the contrary, a few studies have shown an inverse correlation. According to these studies, PSA production decreases with increasing histological grade. The lack of correlation between Gleason score and PSA may be explained by a decrease in antigen production by higher grade lesions due to loss of expression of the gene encoding PSA [34, 35]. Our results are similar to those of Kumari Kavita *et al* [29] who reported no correlation between PSA and GS. Thus an elevated total PSA level is predictive of a malignant tumour but not of its aggressiveness. The probability of having a well-differentiated cancer decreased significantly with increasing PSA level. The results of f/tPSA ratio <15% and >15% in relation to Gleason Score differ with those of Cavit Ceylan *et al* [36] who reported 49.6% of patients with f/tPSA ratio <15% who had well differentiated (SG≤6), moderately differentiated (SG=7) and poorly differentiated (SG ≥8) GS in 65.2%, 14.8% and 20.0% respectively. 50.4% of patients with a ratio >15% had well differentiated (SG≤6), moderately differentiated (SG=7) and poorly differentiated (SG ≥8) GS in 73.0%, 19.7% and 7.3% respectively. This study conducted over a longer period with a more representative sample marks a difference to ours and we found that f/tPSA ratios decreased in the majority of patients with higher Gleason scores.

Diagnostic evaluation of the efficacy of different PSA derivatives

Analysis of the AUC/ROC curve indicated that the f/tPSA ratio was more predictive of prostate cancer. Pourmand *et al* [9], Xue-Dan *et al* [15], Houshang

Amirrasouli *et al* [21] reported similar results for the respective AUCs of the f/tPSA ratio (AUC, 0.80, 0.79, 0.69) more predictive of prostate cancer than the AUCs of tPSA (AUC, 0.78, 0.71, 0.60) and fPSA (AUC, 0.59, 0.63, 0.55). The predictive accuracy of the f/tPSA ratio observed in our study has also been reported by many authors and is consistent with the literature [9, 15, 21]. The results of the diagnostic evaluation of the different PSA derivatives in the 4ng to 10ng tPSA range differed from those of Xue-Dan *et al* [15] who reported in the 4ng to 10ng tPSA range a higher AUC/ROC for f/tPSA (95% CI, AUC, 0.76) than for tPSA (95% CI, AUC, 0.55) and fPSA (95% CI, AUC, 0.25). This difference may be explained by the small sample sizes in this group. Houshang Amirrasouli *et al* [21] believe that setting an appropriate cut-off value for the f/tPSA ratio is crucial, as it may allow better detection of prostate cancers; they reported that when the f/tPSA cut-off value was 12, sensitivity and specificity were 76% and 71% respectively and detected 76% of cancers, but subjected 39% of cancer-free men to prostate biopsy; when it was 14, sensitivity increased to 83%, but specificity fell to 61% and it improved by detecting 83.5% of cancer patients with a false positive rate of 49%.

Safarinejad MR *et al* [37] reported that when the f/tPSA cut-off value was between 15 and 18, it increased the sensitivity for cancer detection from 85.2% to 94.5%, while false positives decreased by 30.8%. Pourmand *et al* [9] reported that when the f/tPSA threshold was 15, sensitivity was approximately 99% for CaP. Several studies have reported that f/tPSA is one of several PSA-related markers useful for suggesting prostate biopsy in patients with intermediate levels of tPSA and when a 15% f/tPSA cut-off was used as a criterion for biopsy, 54% of cancers were detected [24-25]. The high threshold value of tPSA and f/tPSA observed in the general population in our study compared with other studies may be explained by the fact that most of these studies were conducted in patients with total PSA levels below 10ng/ml and 25ng/ml, in contrast to the threshold value of tPSA and f/tPSA in our study of patients with tPSA levels between 4 and 10ng/ml, which is consistent with other studies.

CONCLUSION

The contribution of the new biomarkers to the early diagnosis of prostate cancer was considerable in our study. The percentage of the f/tPSA ratio below 15% is associated with the development of prostate cancer and this ratio is more predictive of PCa than tPSA and fPSA. The variability in the diagnostic accuracy of the different PSA derivatives not only allowed us to obtain threshold values but also to identify the number of biopsies that could be avoided.

ACKNOWLEDGMENTS

To the Director General, the Head of the Urology Department and the staff of the Brazzaville University and Hospital Center for supporting me and providing me with all the resources necessary for the completion of this work.

AUTHORS'CONTRIBUTIONS

Designed the study: DM and OAWS. Performed the analysis: LSBS. Analyzed the data: LSBS, LVG and MC. Contributed patients, reagents and statistical analysis: MFG, OAWS, LVG, DM and AAA. Wrote the paper: LSBS and LVG.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

STUDY LIMITATIONS

The limitation of the study was the small sample size.

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Cite This Article: Loungouala Sounda Bernaud Sedwige, Loubano Voumbi Ghislain, Mouamba Fabien Gael, Odzebe Anani Wencesl Severin, Moukouma Constantin, Moukassa Donatien, Abena Ange Antoine (2023). Diagnostic Performance of the Free to Total PSA Ratio in the Detection of Prostate Cancer in Patients Over 50 Years of Age at the Brazzaville Hospital Center, Congo. *EAS J Biotechnol Genet*, *5*(4), 75-82.