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Reliability of PSA assays: A key asset for early prostate cancer detection

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Abstract

Introduction: Prostate cancer requires early detection to reduce mortality, with PSA serving as a key marker since 1987. This assay, crucial for distinguishing benign conditions from cancer, requires rigorous precision in the laboratory. The aim of this study was to verify the method of PSA measurement in the biochemistry laboratory of the CHU Mohammed VI d'Oujda.

Materials and methods: This prospective study, conducted at the CHU Mohammed VI d'Oujda over 30 days, assessed the reliability of total and free PSA measurements on the Abbott Alinity ci® analyzer. It assessed reproducibility through multi-operator tests and repeatability through consecutive analyses of standardized samples. The CMIA method enabled rigorous quantitative measurement, with analysis of coefficients of variation compared to CLSI standards to guarantee precision and accuracy, validated by intermediate management software.

Results: The study assessed the repeatability and reproducibility of total and free PSA assays at different concentration levels. The results indicate that the majority of values fall within the acceptable range of variation ([-1S, 1S]), although minor variations were observed depending on levels and handling conditions. These results confirm the accuracy of the assay methods and underline their reliability for robust clinical analyses.

Discussion and conclusion: Our results demonstrate good repeatability and reproducibility of tPSA and fPSA assays on Abbott's Alinity ci® analyzer, in line with performance standards established in the literature.

Keywords: Early detection; Prostate cancer; PSA; Repeatability; Reproducibility

1. Introduction

Early detection of prostate cancer (PCa), a disease with a high incidence and prevalence, is an area of research that is helping to reduce morbidity and mortality (1). The discovery in 1987 of prostate-specific antigen (PSA) as a tumor marker revolutionized prostate cancer screening, which had previously relied mainly on prostatic acid phosphatase detection and digital rectal examination (DRE) (2). In 1994, the Food and Drug Administration (FDA) approved the PSA assay for prostate cancer screening, with a cut-off value of 4 ng/mL. Since then, PSA has become a valuable prostate cancer marker, widely used for screening, diagnosis and follow-up of prostate cancer patients (3).

Total PSA (tPSA) comes in two main forms: free PSA (fPSA) and complexed PSA (cPSA). Around 30% of circulating tPSA in serum is present as free PSA, while 70% is complexed. fPSA tends to increase in benign prostatic hyperplasia (BPH),

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while cPSA is often higher in patients with prostate cancer, making it possible to distinguish these two pathologies (4, 5).

Repeatability and reproducibility (intermediate precision) tests are essential for assessing the accuracy and reliability of automated laboratory systems in medical biology. Intermediate precision, or intra-laboratory reproducibility, makes it possible to test a sample under different conditions (e.g., with different operators or reagents), in order to set acceptance criteria based on previous data and biological variations.

Given the importance of PSA in the diagnostic approach to prostate cancer, it is incumbent on medical laboratories to guarantee reliable and accurate results in line with international standards. To meet these standards, the present study aims to verify the PSA measurement method at the Biochemistry Laboratory of the CHU Mohammed VI d'Oujda.

2. Materials and Methods

This prospective study, carried out at the biochemistry laboratory of the CHU Mohammed VI d'Oujda over 30 days, aimed to assess the reliability of free PSA (fPSA) and total PSA (tPSA) assays. In accordance with COFRAC's technical guide to accreditation (SH GTA 04), the study was divided into two distinct phases to ensure the accuracy and robustness of the results. The first phase assessed the reproducibility of the results produced by the analyzer. Control samples, divided into three concentration levels (low, medium and high), were tested daily by different operators for 30 days, in accordance with the manufacturer's instructions. This approach made it possible to verify the consistency of results under various handling conditions. The second phase consisted in testing repeatability using the same samples without time intervals or operator changes, thus eliminating potential variability factors linked to handling. Serum samples were collected and divided into three groups of tPSA and fPSA concentrations covering the entire measurement spectrum. Each sample was then analyzed 30 consecutive times. PSA assays were performed on the Abbott Alinity ci® analyzer using a two-step CMIA immunoassay for the quantitative measurement of total and free PSA. After incubation of the sample with paramagnetic microparticles coated with anti-PSA antibody, an acridinium-labeled anti-PSA antibody was added to create a chemiluminescent reaction measured in light units (RLU), directly related to PSA concentration. Data were analyzed using BYG Informatics' EVM intermediate software, which links the analyzer results to the iLab validation software. To guarantee the reliability of results, coefficients of variation were compared with Clinical & Laboratory Standards Institute (CLSI) standards.

3. Results

3.1. Repeatability

Table 1 Results of the Total and Free PSA Repeatability

	CONTROL SAMPLES	NUMBR(n)	MEAN(M)	STANDARD DEVIATION(s)	CV
tPSA	Low level	30	0.67	0.021	3.22 %
	Medium level	30	3.31	0.139	4.21 %
	High level	30	22.73	1.339	5.89 %
fPSA	Low level	30	0.36	0.011	3.00 %
	Medium level	30	1.70	0.082	4.79 %
	High level	30	10.12	0.283	2.80 %

In the analysis of total PSA repeatability for the low level, 70% of values (21/30) fell within [-1S, 1S], 10% (3/30) within [1S, 2S] and 20% (6/30) within [-2S, -1S]. For the medium level, 63.33% of values (19/30) were in the [-1S, 1S] zone, 13.33% (4/30) in the [1S, 2S] zone, 20% (6/30) in the [-2S, -1S] zone and 3.33% (1/30) in the [2S, 3S] zone. Finally, for the high level, 70% of results (21/30) were in [-1S, 1S], 10% (3/30) in [1S, 2S], 16.67% (5/30) in [-2S, -1S] and 3.33% (1/30) in [2S, 3S] (Table 1, Figure 1).

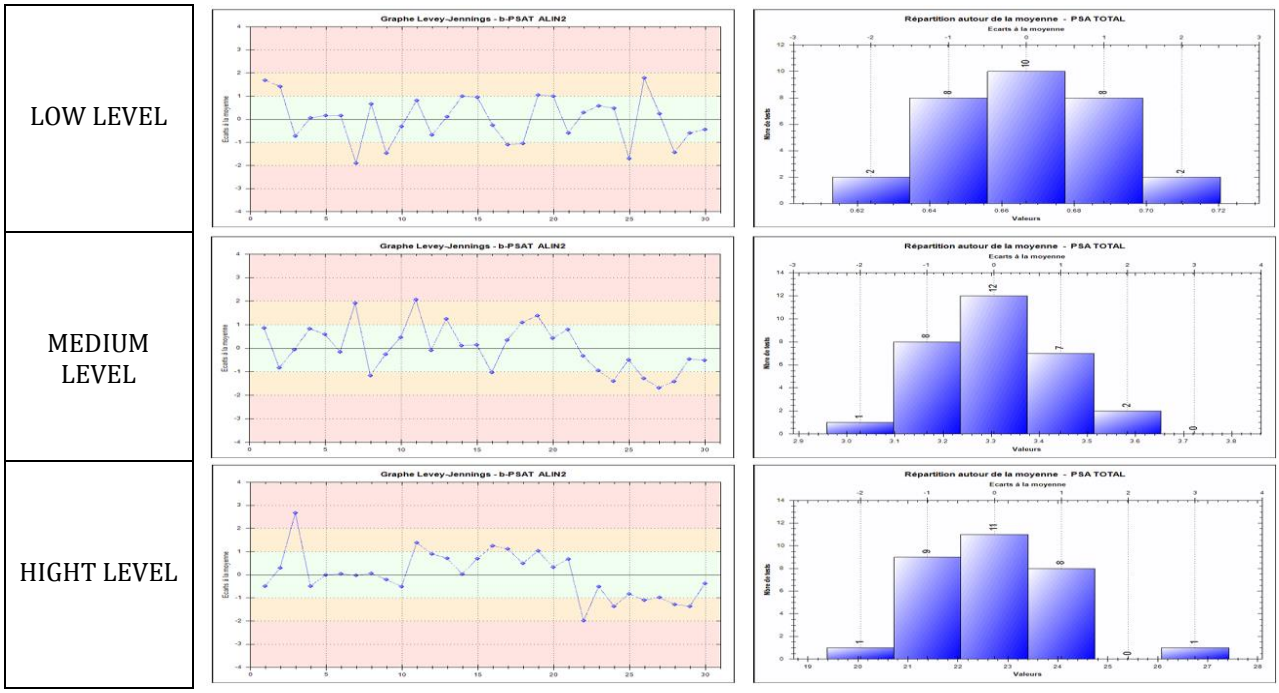

Figure 1 Levey-Jennings graphs for the Repeatability of the Three Levels of Total PSA

As regards the repeatability of free PSA, for the low level, 63.33% of values (19/30) fell within [-1S, 1S], 23.33% (7/30) within [1S, 2S] and 13.34% (4/30) within [-2S, -1S]. For the medium level, 70% of values (21/30) were in the [-1S, 1S] zone, 10% (3/30) in the [1S, 2S] zone, 16.67% (5/30) in the [-2S, -1S] zone and 3.33% (1/30) in the [-3S, -2S] zone. For the high level, 63.33% of values (19/30) were in [-1S, 1S], 13.33% (4/30) in [1S, 2S], 16.67% (5/30) in [-2S, -1S], and 3.34% (1/30) in [-3S, -2S] (table 1, figure 2).

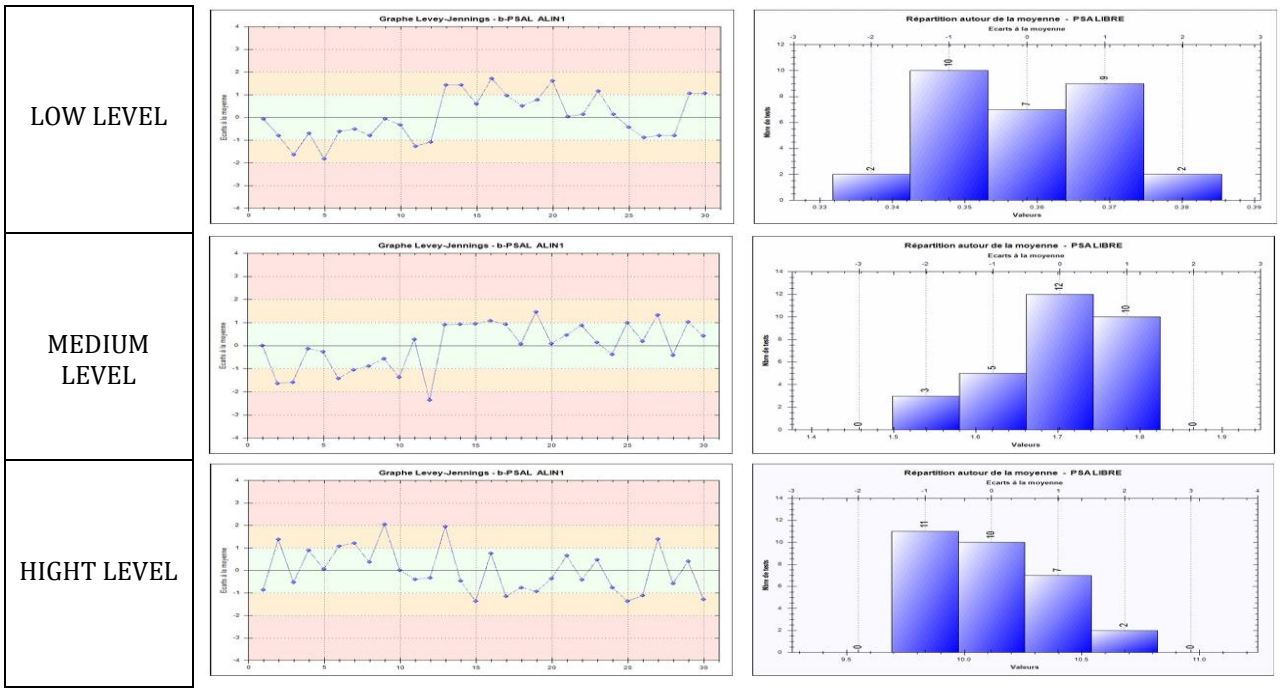

Figure 2 Levey-Jennings graphs for the repeatability of the three PSA free levels

3.2. Reproducibility

Table 2 Results of the Reproducibility of Total and Free PSA

	CONTROL SAMPLES	NUMBR(n)	MEAN(M)	STANDARD DEVIATION(s)	CV
tPSA	Low level	30	0.66	0.024	3.69 %
	Medium level	30	3.25	0.139	4.29 %
	High level	30	21.32	0.902	4.23 %
fPSA	Low level	30	0.37	0.018	4.88 %
	Medium level	30	1.84	0.068	3.73 %
	High level	30	11.40	0.374	3.28 %

When total PSA reproducibility was assessed, 56.67% of values (17/30) fell within [-1S, 1S], 23.33% (7/30) within [1S, 2S] and 20% (6/30) within [-2S, -1S] for the low level. For the medium level, 66.66% (20/30) of values were in the [-1S, 1S] zone, 16.67% (5/30) in the [1S, 2S] zone and 16.67% (5/30) in the [-2S, -1S] zone. Finally, for the high level, 60% of values (18/30) were in [-1S, 1S], 23.33% (7/30) in [1S, 2S] and 16.67% (5/30) in [-2S, -1S] (Table 2, Figure 3).

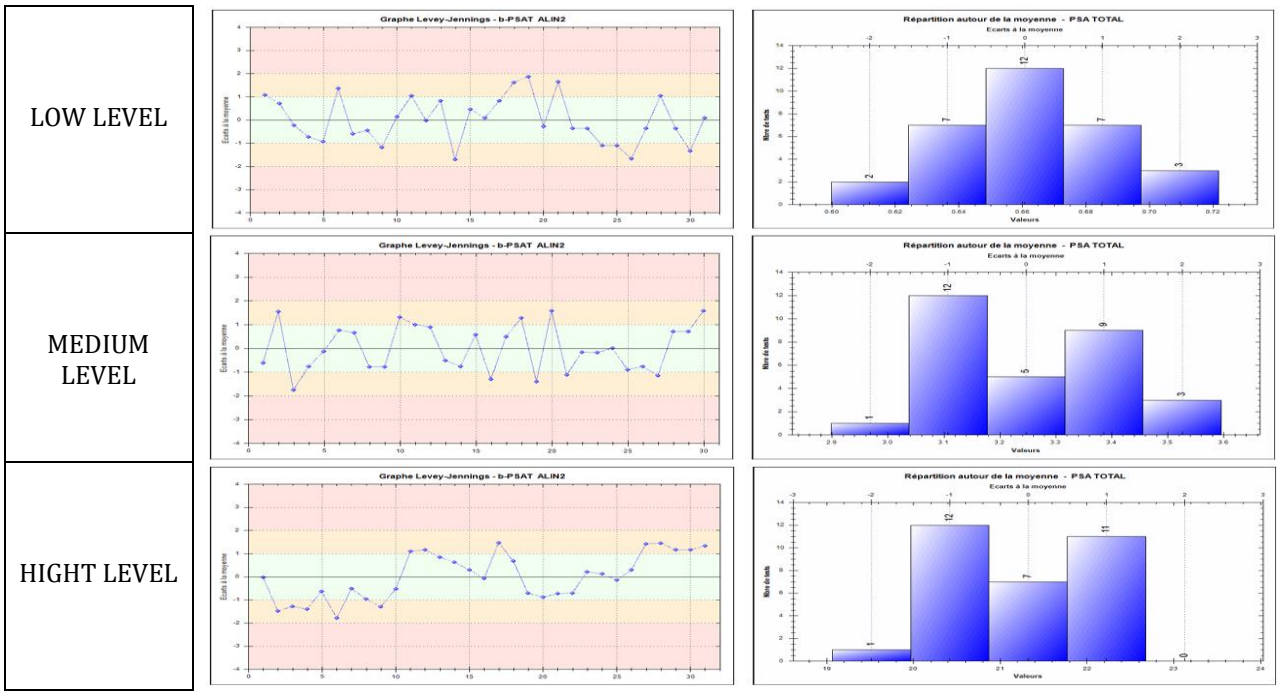

Figure 3 Levey-Jennings graphs for the Reproducibility of the Three Levels of Total PSA

As regards reproducibility of free PSA, 63.33% of values (19/30) fell within [-1S, 1S], 16.67% (5/30) within [1S, 2S], 16.67% (5/30) within [-2S, -1S] and 3.33% (1/30) within [-3S, -2S] at the low level. For the medium level, 76.67% (23/30) of values were in [-1S, 1S], 3.33% (1/30) in [1S, 2S], 10% (3/30) in [-2S, -1S], 3.33% (1/30) in [2S, 3S], and 6.67% (2/30) in [-3S, -2S]. Finally, for the high level, 46.67% of values (14/30) were included in [-1S, 1S], 23.33% (7/30) in [1S, 2S] and 30% (9/30) in [-2S, -1S] (Table 2, Figure 4).

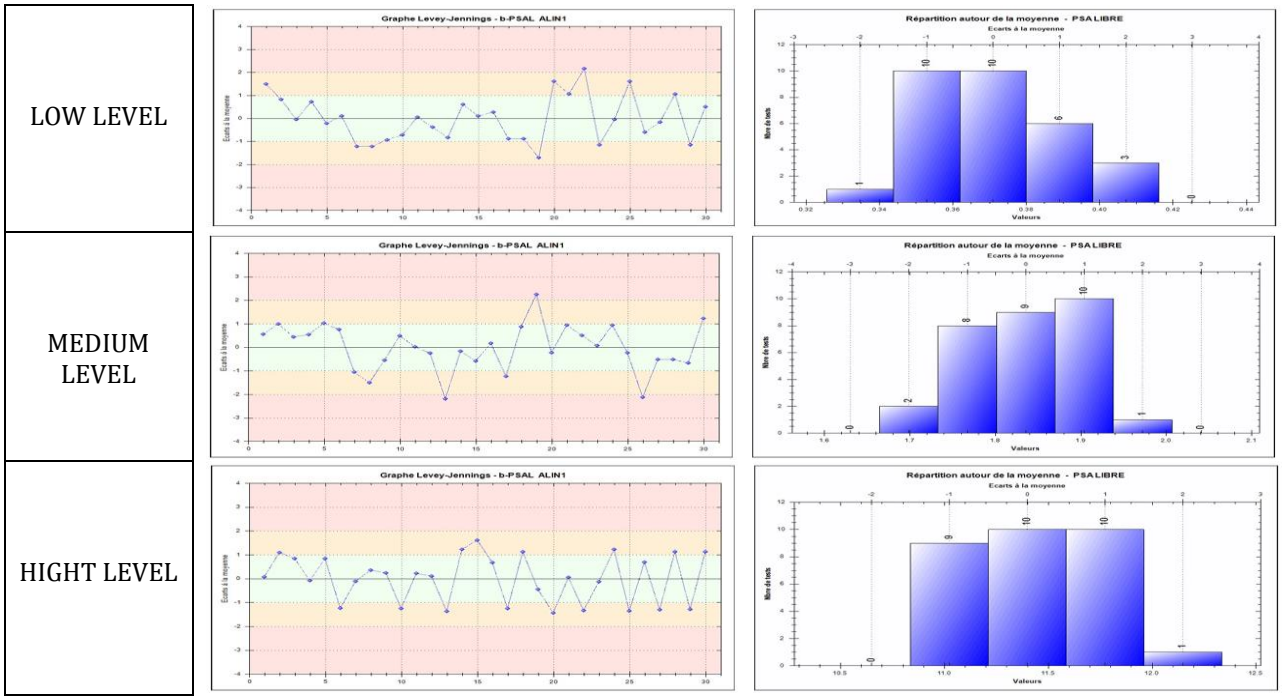

Figure 4 Levey-Jennings graphs for the Reproducibility of the Three Levels of Free PSA

These results confirm the accuracy of methods for measuring total and free PSA, while identifying variations between concentration levels and handling conditions.

4. Discussion

Serum PSA (prostate-specific antigen) measurement is an essential tool for screening and monitoring prostate cancer. A total PSA (PSAt) level above 4.0 ng/ml is generally associated with an increased risk of prostate malignancy, warranting biopsy (4). Furthermore, in patients with prostate cancer, the free fraction of PSA is significantly reduced compared to the total fraction, in contrast to patients with benign prostatic hyperplasia (3). Available immunoassay systems allow simultaneous quantification of free PSA and the form complexed with α1-antichymotrypsin, in order to accurately determine total and free PSA concentrations (5).

Precision represents the degree of agreement between repeated measurements of the same sample or similar samples under specified conditions. It is often expressed by imprecision, calculated using the standard deviation and coefficient of variation. This evaluation is a critical step in validating or verifying a method to ensure its suitability for the intended use. According to ISO 15189, laboratories must have a procedure for method verification before use to ensure that their performance meets manufacturer specifications. The precision evaluation includes repeatability and intermediate reproducibility, in accordance with recommendations such as those from SH GTA 04 by COFRAC and EP15-A3 by CLSI (6).
Our results show good repeatability and reproducibility for tPSA and fPSA assays, with the majority of values falling within the established confidence interval for each concentration level (low, medium, high). These performances align with the target coefficient of variation (CV) values defined by the Clinical & Laboratory Standards Institute (CLSI) and are comparable to the analytical objectives set by SFBC (6–8). The low CV values indicate that even when different factors such as operator or reagent lot are modified, the test consistently produces results close to the average value. The inter-sample contamination approach proved satisfactory for routine use.

Other studies, notably that of Hernández et al. (2004), have also demonstrated that chemiluminescence-based assays on similar platforms exhibited low intra-analytical variability, particularly for tPSA. In their study, they observed that tPSA values mostly remained within the [-1S, 1S] interval during repeated tests over multiple days and with different operators, corroborating our findings on consistency across various experimental conditions (multiple operators and spaced testing periods) (9).

Conversely, some authors have reported slightly higher variability for fPSA. For instance, The National Cancer Institute Surveillance et al. (2016) observed that tPSA measurements were more sensitive to operator-dependent variations, occasionally exceeding analytical target CVs (10). Although our results show slightly increased variability for low-level fPSA compared to tPSA, the overall precision remains within acceptable limits. These minor differences may be explained by the sensitivity variations of the CMIA method for fPSA, due to the more labile molecular structure of free PSA.

Finally, the differences between our results and some higher variability values observed in other studies may also be attributed to calibration protocols and the quality of reagent kits used. As noted by Loeb et al. (2012), PSA assay consistency can be improved through regular calibration and rigorous quality control measures (11).

5. Conclusion

In conclusion, our results demonstrate good repeatability and reproducibility of tPSA and fPSA assays on the Abbott Alinity ci® analyzer, in agreement with established performance standards in the literature. The use of CMIA-based immunoassay technology provides reliable and consistent results, even under varied operational conditions. These observations highlight the importance of a strict protocol and regular quality controls to maintain diagnostic precision while emphasizing the robust performance of the analytical platform for PSA detection in human serum samples.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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