Evidence for the use of the Alere Afinion™ AS100 for measuring the levels of C-reactive protein in an elderly South African population

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Introduction: This study evaluated the performance of the Alere Afinion™ AS100 analyser for the measurement of C-reactive protein (CRP) levels in a population of older adults from South Africa.

Methods: This study was a sub-study of the Sexual Health, HIV infection and comorbidity with non-communicable diseases among Older Persons (SHIOP) study. The median age of SHIOP participants was 61 years (interquartile range 12). Serum samples collected through SHIOP were used to measure CRP levels on the Alere Afinion™ AS100 (Point-of-care) and ABX Pentra 400 (reference method), respectively. Bland–Altman analysis and Lin’s concordance correlation coefficients were used to assess the agreement between the two analysers.

Results: A total of 183 serum samples were tested in the study. The Alere Afinion™ AS100 median values for CRP were 9.5 mg/L and 11.5 mg/L in women and men respectively ($p = 0.275$). The ABX Pentra 400 median levels were lower with 5.6 mg/L and 3.6 mg/L for women and men ($p = 0.027$), respectively. Bland–Altman analysis and linear regression analysis showed an excellent correlation between the Pentra and Afinion analysers, with a Lin’s concordance correlation coefficient of 0.971. The Alere Afinion™ AS100 was able to correctly classify > 90% (165/183) of the CRP results when compared to the ABX Pentra 400.

Conclusion: This study showed that the Alere Afinion™ AS100 had an excellent correlation with a standard laboratory method. However, the Afinion™ AS100 did not correlate well at elevated CRP levels. This may not be clinically significant since the cut-points for CVD risk are at much lower levels.

Keywords: C-reactive protein, Afinion, Pentra, performance, concordance correlation, South Africa

Introduction

Evidence has shown that C-reactive protein (CRP) levels are able to predict the risk of a variety of cardiovascular outcomes such as acute myocardial infarction (AMI), sudden cardiac arrest and peripheral arterial disease.¹ The global probability of dying from myocardial infarction, stroke, cancer, chronic respiratory attacks and diabetes in 2016 was 18%, with a slightly higher risk for males (22%) than for females (15%).² In South Africa, studies show the increased prevalence of cardiovascular disease risk factors in aged populations including hypertension, lipidaemia and cardiometabolic biomarkers.^{3–5} Many people are not aware of these risk factors increasing their probability of cardiovascular events and death.⁶ A previous study has shown that there is a close link between elevated serum CRP levels and increased vulnerability for disease and mortality in older patients.⁷ CRP has been found to be comparable to other confirmed cardiovascular risk factors namely, diabetes and hypertension.⁸

The lack of laboratory testing to identify biomarkers associated with disease may have resulted in the high mortality

rates associated with cardiovascular events.⁹ Most developing countries often lack laboratories with state-of-the-art automated analysers that offer laboratory results that are highly reproducible, accurate and highly sensitive.⁹ Delivering health care in these areas is a major challenge due to unavailability of clean running water and dependable electrical services.¹⁰ In order to overcome these limitations, it is crucial that fast and easy to use point-of-care tests (POCTs), that can significantly increase clinicians’ proficiency to diagnose patient diseases quickly and accurately, are implemented.^{11,12}

There is an increase in the demand of patients seeking treatment at local clinician’s offices thereby contributing to POCTs becoming one of the fastest growing areas of biomedical technology.¹³ The Afinion™ AS100 analyser (Alere, South Africa) is a compact bench-top, multi-assay POC analyser. The turnaround time from sample collection to results being available to the patient is < 30 minutes.¹⁴ Jain et al.¹⁵ confirmed that the Afinion™ AS100 analyser provides a platform for the analysis of multiple analytes with good comparability to the standard laboratory method (Cholestech LDX). Kvam et al.¹⁶ also found

that the Afinion™ AS100 was able to produce a good correlation when compared to another POCT DCA2000 for microalbumin/creatinine as well as when compared to the automated laboratory modular albumin and creatinine methods. Abbai et al.¹⁴ recently found a good correlation between the Alere Afinion™ AS100 analyser and the ABX Pentra 400 analyser for the measurement of glycated haemoglobin (HbA1c) and lipid levels in older adults in Durban, South Africa.

Of the abovementioned studies, none have evaluated the diagnostic performance of the Afinion™ AS100 analyser when compared to a standard laboratory test for the determination of CRP levels. There is, therefore, a dearth of studies on the performance of point-of-care analysers compared to standard laboratory methods in the measurement of CRP, especially in sub-Saharan African older adults. This study evaluated the Alere Afinion™ AS100 analyser (Alere, South Africa) against the ABX Pentra 400 analyser for the measurement of CRP levels in elderly men and women aged 50 years and older from South Africa.

Methods

Ethical approval

This study was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (BE074/17), and the parent Sexual Health, HIV infection and comorbidity with non-communicable diseases among Older Persons (SHIOP) study was approved by the South African Medical Research Council Ethics Committee (ECO30-9-2015).

Study design and population

The study was a sub-study of a larger study, SHIOP. The SHIOP study was a cross-sectional study conducted from February to April 2016 in men and women aged 50 years and older; median age 61 years (interquartile range [IQR] 12). The primary aim of SHIOP was to describe sexuality, sexual health, HIV and comorbidity with chronic non-communicable diseases in the aged population in a setting of high human immunodeficiency virus (HIV) prevalence.

Sample collection

Participants who enrolled in SHIOP provided venous blood samples for laboratory testing. Blood collection was performed according to Good Clinical Laboratory Practices (GCLP) by a trained nurse. Whole blood was drawn aseptically into a serum separator gel (SST) tube. In order to preserve sample integrity, the serum samples were stored at -80 °C for further testing. A total of $n = 183$ serum samples was available for analysis in this study. Samples were tested on both the ABX Pentra 400 analyser (Horiba Ltd, Kyoto, Japan) (reference analyser) and the Alere Afinion™ AS100 (Abbott, United States) (POCT) for the determination of CRP levels.

Determination of CRP levels using the ABX Pentra 400 (reference analyser)

Testing was performed as per the manufacturer's instructions¹⁷ by a single trained user. In order to ensure valid analytical runs

on the reference method, ABX Pentra Immuno I Control L/H, Ref. A11A01621 ABX Pentra Low CRP Control, Ref. A11A01731 (low and high controls) were used. Both low and high controls were tested daily prior to testing the samples. Internal quality control was performed as per the manufacturer's instructions, the ABX Pentra Immuno I Control L/H was tested daily prior to sample processing in order to check the status of the analyser, to verify that it is in good working condition and that it will produce reliable and good quality results. Internal quality control results were reviewed and checked against expected values. Only when quality control was within the acceptable range were samples tested. Calibration was not performed as the testing of the sample occurred within a month. The manufacturer claims that the CRP reference range for adults (20–60 years) is < 5 mg/L.

Once all maintenance procedures were completed and internal quality controls were run as per manufacturer's instructions, testing was done. Approximately 4.0 µL of serum was used for this assay. The CRP reagents were provided as a ready-to-use kit. No preparation/reconstitution of the reagents was required. During the installation of the reagent cartridge, the CRP reagent door which is located on the right-hand side of the analyser was opened. The CRP reagent kit consisted of R1, R2 and R3, which were all removed from the refrigerator and added to the analyser. The door was closed and it was verified that it was properly closed into its locking device as per manufacturer's instruction. The new CRP sensitivity factors were entered on the analyser by following the instruction manual. Single use cuvettes were added on the analyser. These cuvettes ensured that there was no risk of cross-contamination. Measurements of CRP on the ABX Pentra 400 platform ranged from 0.1 mg/L to 43.8 mg/L, with a median of 5.1 mg/L.

Determination of CRP levels using the Alere Afinion™ AS100 (POCT)

All testing was conducted in accordance with the manufacturer's instructions¹⁸ by a single trained user. Quality control testing was performed to confirm that the Alere Afinion™ AS100 analyser system was working properly and providing reliable results. No problems were experienced with the controls. The measured values of the CRP were always within acceptable limits (5–160 mg/L) as stated in the CRP control package inserts. Controls were stored in the fridge (2–8 °C) as per manufacturer's instructions. The control material was used without waiting for it to reach equilibration to room temperature, as indicated on the reagent package insert. The control was mixed well by inverting the vial 8–10 times before the sample was added. Only Afinion™ CRP controls from Axis-Shield were used as recommended by the manufacturer. The Afinion™ CRP control kit contained assayed human serum controls at two concentration levels of CRP. These were tested prior to sample testing.

As part of routine analyser maintenance, the analyser performed a self-test when switched on. Samples were tested after the analyser had completed the self-test by indicating with a green light that it was ready for use. Unlike the control material, upon removal from storage, the CRP test cartridge was allowed to reach a temperature of 15–30 °C before use, as indicated by

manufacturer's instructions. The cartridge was then labelled with the participant study number. The CRP levels were measured using 1.5 µL of serum. The assay time was ~4 minutes and controls with specific target ranges were included in each assay run.

Data analysis

Data were analysed using Lin's concordance correlation coefficients and the Bland–Altman analysis method to assess agreement of CRP readings between the Alere Afinion™ AS100 analyser and the reference analyser, ABX Pentra 400. Bland–Altman method compared mean differences between the Alere Afinion™ AS100 analyser and reference analyser (mean bias). The 95% limits of agreement between the Alere Afinion™ AS100 and laboratory measurements were also calculated. The Bland–Altman methods were appropriate for this analysis since there were no repeat measurements on each method per participant, i.e. there were two sets of measurements for each participant (one for the Alere Afinion™ AS100 and one for the ABX Pentra 400 method). This showed that the two sets of measurements were independent making this approach suitable for data analysis of this evaluation study. Graphical Bland–Altman plots and scatter plots were used to depict the study findings. Using Lin's concordance correlation coefficients, CRP measurements were categorised as excellent (0.90–1.00), good (0.80–0.89), fair (0.70–0.79), or poor (< 0.69).

Based on available data, the diagnostic cut-off for CRP levels is < 1.0 mg/L for low; 1.0–3 mg/L for moderate; and ≥ 3 mg/L for high-risk of future cardiovascular events.^{19,20} Using these cut-off points for this analysis, CRP levels were categorised as: normal (CRP < 3.0 mg/L) and high/elevated (CRP ≥ 3.0 mg/L) as per Table I. This stratification was done based on the data obtained from the ABX Pentra 400 analyser. The Alere Afinion™ AS100 has a measuring range of 5–200 mg/L, with any readings below 5 mg/L simply labelled as < 5 mg/L. The Afinion™ identified 89 cases with CRP simply marked as < 5 mg/L; these cases were excluded from the Lin's correlation analyses reducing the total number of samples to 94.

Regarding the control variables, age was collected in single years and later categorised into broad age groups 50–59, 60–69 and 70+ for this analysis. Participants were asked which was the highest grade they had completed from grade 1 to 12 or post-high school education according to the South African education system. Education level was then categorised as no formal education, primary (grade 1 to 7), secondary or higher (grade 8 to 12 or college certificate or university degree). Blood pressure was measured using the Healthease digital blood pressure monitor, validated by the European Society of Hypertension to measure blood pressure according to World Health Organization (WHO) standards with cut-points of systolic BP < 120 mm Hg or diastolic BP < 80 mm Hg as normal, systolic BP 120–139 mm Hg or diastolic BP 80–89 mm Hg as pre-hypertensive, and systolic BP ≥ 140 mm Hg or diastolic blood pressure of ≥ 90 mm Hg as hypertensive. For each participant three readings of systolic and diastolic blood pressure with rest intervals of one to two

minutes were taken. An average of the three readings was used to categorise participants as normal, pre-hypertensive or hypertensive, as per above cut-points. As for body mass index (BMI), anthropometric measurements of weight and height were taken for each participant. BMI was computed as weight in kilograms divided by height in square meters. Based on WHO standards, a participant was considered underweight if BMI < 18.5, normal (BMI 18.5 to 24.9), overweight (BMI 25 to 29.9) and obese (BMI ≥ 30). Finally, HIV testing using blood specimen collected by venepuncture was undertaken using the Determine HIV-1/2 (Abbott Laboratories, Japan) and Unigold™ Recombigen® HIV rapid tests, as per manufacturer instructions. HIV pre- and post-test counselling was offered to all participants and those testing HIV-positive in the study were linked to care through referral letters to their nearest or choice of clinic.

All analyses were conducted in STATA 14.2 software (StataCorp, 2014).

Results

Overview of the study population

Table I shows some characteristics of study participants overall and by level of CRP as assessed on the ABX Pentra 400 analyser. There were 183 participants for this analysis with a median age of 59 years (IQR 12). Majority of the participants (71%) had high/elevated CRP risk for cardiovascular events (CRP ≥ 3.0 mg/L). Nearly two-thirds of study participants were female (63.4%) compared to males (36.6%). Male participants were slightly older (61 years, IQR 13) than female participants (58 years, IQR 12). Approximately 14.2% of study participants were above 70 years of age, and just over half of the participants were in the youngest age group 50–59 (50.3%). In addition, 65.5% of the study population were overweight or obese; 51.9% were pre-hypertensive; 36.6% hypertensive; and 12.3% were HIV-positive (Table I).

Comparison of CRP levels across both analysers

Serum CRP levels on the Alere Afinion™ AS100 were from < 5 mg/L to 45 mg/L. Excluding values < 5 mg/L, median values for CRP on the Alere Afinion™ AS100 were 9.5 mg/L (IQR 8) and 11.5 mg/L (IQR 12) in women and men respectively (p -value = 0.275). The ABX Pentra 400 median values were 5.6 mg/L (IQR 5.6) and 3.6 mg/L (IQR 6.7) for women and men (p -value = 0.027), respectively. CRP levels, shown as medians with minimum and maximum CRP values by age and gender, were distributed across a wide range on both the Alere Afinion™ AS100 and ABX Pentra 400 analysers as seen in Figure 1; median CRP levels were slightly higher on the Alere Afinion™ AS100 across all ages. However, within the Alere Afinion™ AS100, median values for males were higher compared to median values for females for all ages. In contrast, median values for males on the ABX Pentra 400 were slightly lower than for females by age groups, except for the oldest age group (70+ years).

Diagnostic performance of the Alere Afinion™ AS100 compared to the ABX Pentra 400

The concordance plot of the CRP measurements based on the Afinion™ AS100 and the ABX Pentra 400 analysers is shown in

Table 1: Demographic and health factors of participants in this study⁶

	Total	Normal CRP*	High CRP	p-value
Number of participants	183	53 (29%)	130 (71%)	
Median age (IQR)	59 (12)	62 (13)	58 (12)	
Gender				0.001
Female	63.4	45.3	70.8	
Male	36.6	54.7	29.2	
Age group				0.482
50–59	50.3	43.4	53.1	
60–69	35.5	39.6	33.8	
70+	14.2	17.0	13.1	
Education				0.493
Had no formal education	12.0	7.5	13.8	
Primary	44.8	47.2	43.8	
Secondary or higher	43.2	45.3	42.3	
Blood pressure				0.984
Normal	11.5	5.7	13.8	
Pre-hypertensive	51.9	43.4	55.4	
Hypertensive	36.6	50.9	30.8	
Body mass index (BMI)				0.001
Normal	27.9	47.2	20.0	
Under	6.6	7.5	6.2	
Over	31.1	28.3	32.3	
Obese	34.4	17.0	41.5	
HIV status				0.868
Negative	87.4	86.8	87.7	
Positive	12.6	13.2	12.3	

⁶Table presents percentage distributions in each column based on the number of participants in the table header as the denominator.

* CRP levels were categorised as: CRP < 1.0 mg/L as low, CRP 1.0–3.0 mg/L intermediate, and CRP > 3.0 mg/L high/elevated. These were then re-categorised as Normal (low and intermediate) and High (high/elevated), as presented in this table. The stratification was done based on the data obtained from the ABX Pentra 400 analyser.

Figure 1: Comparison of CRP levels by age and gender. Data are shown as medians (25th and 75th percentile) with minimum and maximum CRP values

Figure 2. The solid black line shows the regression line fitted to the Afinion™ AS100 and ABX Pentra 400 values, whereas the dashed blue line is where the scatter points would be expected to lie if there was perfect concordance in CRP measurements between the Afinion™ AS100 and the ABX Pentra 400 analysers. The Alere Afinion™ AS100 was able to identify 44 samples with CRP measurements above 10 mg/L compared to the 38 identified

by the ABX Pentra 400. Six samples were therefore overestimated by the Alere Afinion™ AS100. The plot shows CRP values from the two analysers lying very close to the regression line of perfect concordance (dashed green line) especially for CRP < 20 mg/L (Figure 2). At higher values, however, there is a positive bias towards CRP measurements on the Afinion™ AS100. That data

Figure 2: Scatterplot of CRP values on the Afinion™ and Pentra analysers with regression lines

Figure 3: Lin's concordance limits of agreement plot showing agreement between the Afinion™ and Pentra analysers

shows an increasing variability as the measurement increases, known as the funnelling out effect.

The Bland and Altman diagram

Given the funnelling out effect highlighted above, we plotted the Bland–Altman using a log transformation of the raw data, which is considered an appropriate approach for handling data showing a linear relationship between paired differences and paired means.^{21,22} The log-transformation of the raw data was able to achieve the normality assumption required for the Lin's concordance analysis. The Bland–Altman plot obtained, shown in Figure 3, shows no funnelling out of the scatter points. However, this plot is difficult to interpret as the output is not on the same scale as the raw data. The results were therefore back-transformed to get the indices shown in Table II.

Indices of reliability

Lin's concordance correlation coefficients were used to assess the agreement between the Alere Afinion™ AS100 and the ABX Pentra 400 analysers. Results are as presented in Table II showing an excellent concordance correlation coefficient of 0.971 (95% CI 0.96; 0.98). Mean bias is the average difference between CRP measurements on the Alere Afinion™ AS100 and the ABX Pentra 400. In our analysis, the mean bias was 1.10 (SD 1.11). That is, readings on the Afinion™ were on average 10% higher than on the ABX Pentra 400. The Bland–Altman (BA) limits of agreement shows that 95% of the differences in the measurements on the Afinion™ were between 10% below the ABX Pentra 400 up to 36% above.

Discussion

A previous study highlighted the need for interventions which address the burden of HIV and non-communicable diseases among older adults in South Africa.¹⁴ In this study, 34.4% of participants were obese according to the BMI calculations taken in this analysis. Evidence that obesity and even excessive weight have a close association with an elevated risk of CVDs has been shown by Csige et al.²³ According to Lavie et al.²⁴ obesity presents many adverse effects on the functioning of the cardiovascular structure.

The prevalence of HIV in the studied population was 12.6%. A study by Post et al.²⁵ suggested that the presence of atherosclerosis caused by a condition such as HIV and its treatment have a high effect in increasing the risk of CVDs among people who are infected with HIV. Some observational cohort studies have also demonstrated increased levels of CVDs in HIV-infected versus control patients, with an approximate 1.5 to 2-fold increased relative risk.^{26–28}

As mentioned earlier, the lack of laboratory testing to identify biomarkers associated with disease may have resulted in the high mortality rates associated with cardiovascular events.⁹ This study evaluated the performance of the Alere Afinion™ AS100 analyser in comparison with the standard laboratory method, the ABX Pentra 400 for the measurement of CRP. This evaluation was performed in an elderly population of HIV-positive and -negative adults. The majority of the participants in this study had high/elevated levels of CRP indicative of their increased risk for future cardiovascular events. This study found that the CRP readings on the Afinion™ AS100 were on average higher than on the ABX Pentra 400 analyser. Despite the Afinion™ AS100 did not correlate well at elevated CRP levels (above 20 mg/L according to Figure 2), this may not be clinically significant since the cut-points for CVD risk are at much lower levels (i.e CRP < 3.0 mg/L is normal and CRP ≥ 3.0 mg/L is high/elevated CVD risk).

Table II: Differences between the Alere Afinion™ AS100 and ABX Pentra 400 CRP measurements using Bland–Altman (BA) plots and Lin's concordance correlation coefficients

CRP	N	Mean bias (SD)	95% BA limits of agreement	Concordance correlation coefficient	95% confidence interval
Overall	94	1.10 (1.11)	(0.90; 1.36)	0.971	(0.960; 0.982)

SD – standard deviation, BA – Bland–Altman, CRP – C-reactive protein

In addition, an excellent concordance correlation between the Alere Afinion™ AS100 and the Pentra 400 for the measurement of CRP levels was observed.

Our findings on the performance of the Alere Afinion™ were supported by other published studies. Verbakel et al.²⁹ provided evidence of the analytical accuracy and user-friendliness of the Alere Afinion™ AS100 as a POC analyser in measuring CRP in children (one month to 18 years) and outpatient adults (18–65 years). A study by Minnaard et al.³⁰ evaluated five CRP POCT devices (Alere Afinion™, NycoCard™ Reader II, Eurolyser Smart 700/340, QuikRead go® and QuikRead®). At the intermediary concentration of (20–100 mg/L), the Alere Afinion™ was the most accurate device. The authors concluded that the Alere Afinion™ showed better correlation when compared to the other three POCTs. The correlation between the POCT and the laboratory standard methods decreased at higher CRP concentrations, resulting in wider confidence intervals around the mean differences at CRP concentrations greater than 100 mg/L. This is consistent with our findings of increasing variability and confidence intervals above 20 mg/L.

In a later study, Brouwer and Van Pelt³¹ performed a comparison study of six quantitative POCT devices (QuikRead go®, Smart Eurolyser, Afinion™, Ichroma™, Microsemi) and two semi-quantitative methods to measure CRP. A practical evaluation for the six analysers was performed in a laboratory setting, where the main aim of the study was to evaluate the minimum amount of material required, analytical range, pre-analytical handling of the samples and estimated pre-analytical time. In that evaluation it was concluded that the Alere Afinion™ AS100 required the least pre-analytical handling which was less than a minute.³¹ The researchers concluded that the Alere Afinion™ AS100 and the Eurolyser were the preferred analysers for CRP POC testing.

This analysis is not without its limitations. The Afinion™ AS100 has a measuring range of 5–200 mg/L. Measurements < 5 mg/L ($n = 89$) could not be used in the correlation analyses limiting our sample from 183 to 94 participants. Use of the Afinion™ AS100 is therefore limited in clinical practice when patient CRP levels are very low. Generalisability to other settings such as hospital care and younger populations including children is limited as this analysis was not based on a random representative sample. This, however, was the first study to examine the performance of the Afinion™ AS100 relative to a standard laboratory method in measuring CRP in a sample of HIV-positive and HIV-negative elderly people in a sub-Saharan African country.

Conclusion

Presently there is lack of data on POCTs for the measurement of CRP levels, especially in a South African population. This study was the first to evaluate the performance of the Alere Afinion™ AS100 for the measurement of CRP in a population of HIV-negative and HIV-positive older adults (50 years and above) in a high HIV setting. Our findings showed an excellent concordance correlation between the Alere Afinion™ AS100 analyser and the reference laboratory analyser, the ABX Pentra 400 for the measurement of CRP levels. The Alere Afinion™ AS100 is a

simple, robust, convenient and safe analyser.¹⁶ Furthermore, the Alere Afinion™ AS100 may be a good POC analyser for screening in older adults within a high HIV prevalence setting for early detection and diagnosis of cardiovascular diseases.

Acknowledgements

We thank all the men and women who participated in the SHIOP study, and the SHIOP study teams at the SAMRC HIV Prevention Research Unit in Durban.

Author contributions

IBM, MN and NSA developed the concept and performed the data interpretations, MN completed the statistical analysis.

Funding

This study was supported by the South African Medical Research Council (SAMRC) seed funding.

Conflict of interest

None.

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