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ORIGINAL ARTICLE

Verification of a Benchtop Hematology Analyzer with a 5-Part Differential Count: There is Nothing Wrong with Being Small

Anima Baiden, Elise Schapkaitz, Maynolia Naidoo, Susan Louw

Department of Molecular Medicine and Hematology, School of Pathology, Faculty of Health Sciences, University of The Witwatersrand (Wits) and National Health Laboratory Service (NHLS), Johannesburg, South Africa

SUMMARY

Background: **The benchtop ADVIA 560 AL® hematology analyzer (Siemens® Healthineers Tarrytown, NY, USA) offers a small footprint and ease of operation making it suitable for satellite laboratories and intensive care units. A verification study of this analyzer was performed.**
Methods: **Between- and intra-run precision, carry-over, linearity, and throughput were evaluated on the ADVIA 560 AL®. Accuracy was assessed on 94 patient samples by comparing the results obtained on the ADVIA 560 AL® to the results on the reference Sysmex XN1000® analyzer (Sysmex® Corporation, Kobe, Japan).**
Results: **The ADVIA 560 AL® showed acceptable imprecision on control material and minimal bias in comparison to the XN 1000® on patient samples with a throughput of 60 samples per hour. The percentage carryover was not significant and the linearity was within acceptable limits.**
Conclusions: **The ADVIA 560 AL® bench-top analyzer is suitable for acute care centers and satellite laboratories owing to its small footprint, ease of use, and reproducible and accurate results.**
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Correspondence:
Dr. Susan Louw
P.O. Box 94
Cresta, Gauteng, 2118
South Africa
Phone: +27 (82) 606 3487
Fax: +27 866 99 99 01
Email: Susan.louw@nhls.ac.za
ORCID https://orcid.org/0000-0002-4315-1496
Anima Baiden
ORCID https://orcid.org/0000-0001-6912-8617
Elise Schapkaitz
ORCID https://orcid.org/0000-0002-1534-2930
Maynolia Naidoo
ORCID https://orcid.org/0000-0002-1195-9992

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KEYWORDS

benchtop hematology analyzer, 5-part differential count, verification, satellite laboratories

INTRODUCTION

During the Coronavirus disease 2019 (COVID-19) pandemic, the utility of hematological, coagulation and biochemical parameters as predictors of the severity of infection were established [1]. Components of the full blood and differential counts (FBC and DIFF) including low platelets [2], low hemoglobin [3], and changes in white blood cell subtypes, namely lymphopenia and neutrophilia, were predictive of the outcomes of patients with COVID-19 [4].
It was against this background that the National Health Laboratory Service (NHLS) in South Africa validated testing platforms for acute care centers and satellite laboratories [5]. The automated ADVIA 560 AL® (Siemens® Healthineers, Tarrytown, NY, USA) is a small (height, 52 cm, width, 41 cm, and depth, 49 cm) bench-

top analyzer that offers improved turnaround times owing to the suitability for near-patient-testing to assist with emergency patient management. The analyzer has a throughput of 60 samples per hour, and a result can be generated within 60 seconds on emergency samples which can be processed without completing the analysis of samples in the auto-loader tray [6]. Furthermore, it can be connected to a printer, interfaced with a laboratory information system and a handheld bar-code reader is available. A volume of only 110 µL, excluding dead volume, is required for open and closed mode analyses. The analyzer stores up to 100,000 patient results as well as quality control (QC) and calibration results including graphical scatter diagrams and histograms. The ADVIA 560® analyzer is compatible with ethylenediaminetetraacetic acid (EDTA) sample tubes, such as Becton Dickinson (BD)® vacutainers, and pediatric samples in Sarstedt Monovette® tubes. The instrument uses impedance variation to measure the red blood cell and platelet count and optical flow-cytometry for the white blood cell and DIFF counts. Many small benchtop FBC analyzers offer a 3-part DIFF but the ADVIA 560® analyzer performs a 5-part DIFF consisting of lymphocytes, monocytes, neutrophils, eosinophils, and basophils. The hemoglobin is measured by spectrophotometry.

MATERIALS AND METHODS

Ethics
Ethics approval for the study was obtained from the Human Research Ethics Committee (HREC) of the University of the Witwatersrand (Protocol M1911201).

Analyzer
The ADVIA 560® analyzer was installed and calibrated by the manufacturer and laboratory staff received operator training. This study was performed in accordance with the ISO 15189 International Standard for Medical Laboratories, the International Committee on Standardisation in Hematology (ICSH 2014), and the Clinical and Laboratory Standards Institute (CLSI 2010) method comparison guidelines [5,7].

Samples
Commercial controls and residual blood specimens from 94 samples with normal and abnormal hematology profiles submitted for testing at Charlotte Maxeke Johannesburg (CMJAH) and Chris Hani Baragwanath (CHBAH) Academic Hospitals in Johannesburg, South Africa, were included in the study. Patient samples with possible interfering substances, such as lipids and bilirubin as well as hemolyzed samples were included. Fifty-one samples were from patients who were investigated for COVID-19, and of these, 35 (69%) were positive on real-time polymerase chain reaction (PCR) for this viral infection. Patient samples were collected in K2EDTA tubes (Vacutainer®, Becton Dickinson, Plymouth, UK) and stored at room temperature until analysis by a dedicated technologist within 8 hours of collection at the CMJAH, NHLS laboratory [8]. Pediatric samples were excluded from the study since the ADVIA 560 AL® analyzer is not compatible with microtainers, which are the collection tubes utilized for pediatric patients at CMJAH and CHBAH.

Precision
Between-run precision was assessed with commercial controls (high, low, and normal) processed daily for 10 days. Within-run precision was assessed with commercial controls processed 20 times in both the closed automated and open manual mode. Different lots of control material to the internal quality control were used. The mean, standard deviation (SD), and coefficient of variation (CV) were collated on an Excel® spreadsheet and compared to state of the art (SOTA) and manufacturer precision limits [7,9].

Comparison study
Ninety-four samples covering the range of FBC parameters as per ICSH [7] recommendation, were analyzed on both the ADVIA 560 AL® and the already validated Sysmex XN 1000® (Sysmex® Corporation, Kobe, Japan) automated hematology analyzers. The ADVIA 560 AL® DIFF and morphological flags were compared with manual smear evaluation by 2 morphologists on 40 samples as per the ICSH criteria for grading of peripheral blood morphology [10]. Bland-Altman method comparison and regression analyses, with a statistical significance of $p < 0.05$, were performed.

Linearity
Linearity was assessed with serial normal saline dilutions (1:2; 1:4; 1:8, and 1:16) of a patient's samples followed by duplicate analysis.

Carryover
Carryover from a patient sample with high counts to a sample with low counts was assessed by analyzing the high count sample 3 times (H1, H2, and H3) followed by 3 consecutive analyses of the low count sample (L1, L2 and L3). Carry-over was calculated with the following formula: Carryover (%) = (L1 - L3)/(H3 - L3) x 100.

Throughput
Throughput of the auto-sampler for FBC and DIFF was assessed with 60 patient samples analyzed as a batch. The samples were loaded on sample racks which hold 10 samples each. Throughput was defined as the time from bar code reading of the first sample to the last sample reaching the output tray.

Table 1. Full blood count and differential count precision results.

Parameter (units)	Observed precision (%)				Manufacturer claim (%)				SOTA (%)		Criteria met
	Within-run		Between-run		Within-run		Between-run		Within-run	Between-run	
	SD	CV	SD	CV	SD	CV	SD	CV	CV	CV	
Full blood count (FBC)											
WBC (10^9/L)	0.21	1.81	0.29	2.20	< 0.18	< 2.7	< 0.20	< 3.4	2.5	2.5	manufacturer; SOTA
RBC (10^{12}/L)	0.05	1.44	0.05	1.59	< 0.11	< 1.7	< 0.13	< 2	1.1	1.1	manufacturer only
HGB (g/L)	0.17	1.58	0.18	1.47	< 2.0	< 2.0	< 0.22	< 2.4	0.9	1.0	manufacturer only
MCV (fL)	0.37	0.41	0.56	0.60	< 1.0	< 1.7	< 1.2	< 2	0.6	0.8	manufacturer; SOTA
RDW (%)	0.26	1.62	0.36	2.26	< 0.4	< 2.5	< 0.45	< 3	2.0	2.0	manufacturer; SOTA
PLT (10^9/L)	8.21	4.24	7.97	3.67	< 23	< 6	< 27	< 7	3	3	manufacturer only
MPV (fL)	0.31	3.16	0.21	2.18	< 0.45	< 8.7	< 0.50	< 10	2.5	2.5	manufacturer; SOTA
Differential count (Diff)											
Percentage (%) of total white blood cell count											
NEU	1.24	2.23	1.74	3.20	< 3.5	-	< 3.5	-	-	-	manufacturer
LYM	0.95	3.08	1.28	4.00	< 3.1	-	< 3.1	-	-	-	manufacturer
MON	0.71	14.72	1.11	21.30	< 2.0	-	< 2.0	-	-	-	manufacturer
EO	0.32	7.29	0.47	10.10	< 2.0	-	< 2.0	-	-	-	manufacturer
BAS	0.01	7.23	0.00	0.00	< 0.5	-	< 0.5	-	-	-	manufacturer
Absolute counts (10^9/L)											
Total WBC	0.15	1.82	0.12	1.49	< 0.16	< 2.7	< 0.16	< 2.7	-	2.5	manufacturer; SOTA
NEU	0.12	2.14	0,17	3.22	-	-	-	-	-	2.5	did not meet SOTA
LYM	0.10	3.77	0.14	5.25	-	-	-	-	-	3.5	did not meet SOTA
MON	0.07	16.08	0.12	20.86	-	-	-	-	-	8.5	did not meet SOTA
EO	0.95	52.48	0.05	9.94	-	-	-	-	-	10	SOTA
BAS	0.00	0.00	0.00	3.90	-	-	-	-	-	20	SOTA

SD - standard deviation, CV - coefficient of variation, SOTA - state of the art, WBC - white blood cell, RBC - red blood cell, HGB - hemoglobin, MCV - mean cell volume, RDW - red cell distribution width, PLT - platelets, MPV - mean platelet volume, NEU - neutrophils, LYM - lymphocytes, MON - monocytes, EO - eosinophils, BAS - basophils, - - parameter target not available.

RESULTS

Precision

Results of the precision study of the FBC and DIFF are presented in Table 1. The ADVIA 560 AL® showed acceptable imprecision for FBC and % DIFF parameters according to the manufacturer's criteria. The absolute counts of neutrophils, lymphocytes, and monocytes did however not meet SOTA criteria [9], and the manufacturer imprecision limits for these parameters were also not available. The results obtained on open vs. closed mode were comparable without statistically significant differences.

Comparison study

The results of the comparison study on 94 patient samples analyzed on the ADVIA 560 AL® and the Sysmex XN 1000® analyzers are depicted in Table 2. The correlations between the ADVIA 560 AL® and the XN 1000® analyzers, with the exception of the mean platelet volume (MPV), were excellent (Table 2 and Figure 1). Mean differences represented by the Bland-Altman sta-

Table 2. Full blood count and differential count accuracy results.

Parameter (units)	SD [a]	R value	Bias %	TEobs	EFLM TEa
Full blood count					
WBC (10^9/L)	0.21	> 0.99	1.94	2.36	± 13.1
RBC (10^{12}/L)	0.05	> 0.99	-3.27	-3.17	± 3.8
HGB (g/L)	0.17	0.99	3.30	3.64	± 3.9
HCT (L/L)	0.52	0.94	-4.01	-2.97	± 3.0
MCV (fL)	0.37	0.94	-1.03	-0.29	± 1.6
PLT (10^9/L)	8.21	0.99	-7.80	8.62	± 10.3
MPV (fL)	0.31	0.84	-29.52	-28.9	± 3.6
Differential count					
NEU (10^9/L)	0.16	0.96	-5.76	-5.44	± 18.6
LYM (10^9/L)	0.10	0.95	-9.55	-9.35	± 14.1
MON (10^9/L)	0.07	> 0.99	-8.16	-8.02	± 17.3
EO (10^9/L)	0.95	0.76	3.53	5.43	± 27.6
BAS (10^9/L)	0.00	0.35	-62.61	-62.91	± 16.9

SD [a] - within-run standard deviation, TEobs - total error observed, EFLM Tea - European Federation of Clinical Chemistry and Laboratory Medicine Total allowable error, WBC - white blood cell, RBC - red blood cell, HGB - hemoglobin, HCT - hematocrit, MCV - mean cell volume, PLT - platelets, MPV - mean platelet volume, NEU - neutrophils, LYM - lymphocytes, MON - monocytes, EO - eosinophils, BAS - basophils.

tistics were small for white blood cell (WBC) and hemoglobin (HGB) with few outliers. For platelets (PLT), however, a mean difference of -21.37 (95% CI, -65.54 to 22.80) was found. The correlation between the manual morphological and automated differential counts was excellent with the exception of the basophil count.

The following 5 morphology flags were triggered on the ADVIA 560 AL® analyzer during the analysis of 40 samples: White blood cell high linearity range exceeded; Monocyte-Neutrophil differentiation; Platelet-red blood cell fragment differentiation; abnormal differential counts and Monocyte-Lymphocyte differentiation. These samples were assessed with manual morphological examination and the false negative rate of the flags was < 5%.

Carryover

The percentage carryover for white blood cells was 0.26%, 0% for hemoglobin and 0.31% for platelets. These results were not significant and within the manufacturer's limit of 1%.

Linearity

The linearity for hemoglobin (44 - 223 g/L), white blood cells (0.29 - 112.92 x 10^9/L), and platelets (3 - 1,006 x 10^9/L) were within acceptable limits for high and low ranges.

Throughput

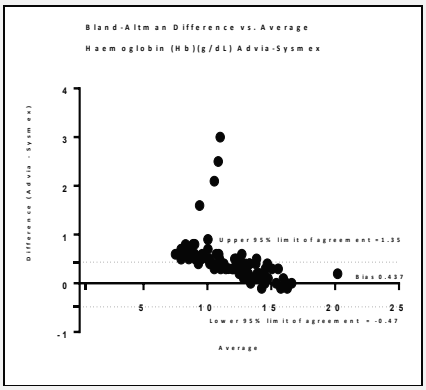
The throughput for 60 samples was 62 minutes for FBC-DIFF analysis.

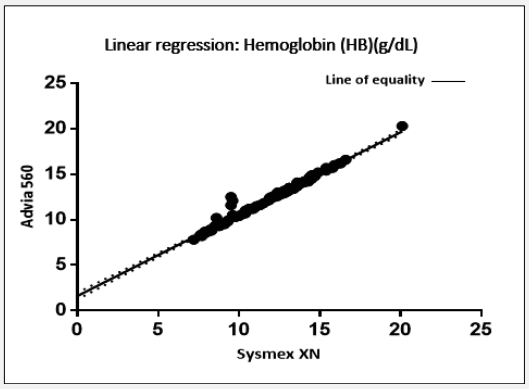
DISCUSSION

The ADVIA 560 AL® hematology analyzer is suitable for sample analysis in clinical settings such as emergency departments, critical care units, and field hospitals since this analyzer has a small footprint, requires minimal operator expertise and maintenance while producing accurate and reproducible results.

In this study, the performance of the ADVIA 560 AL® automated analyzer was compared with the reference large benchtop Sysmex XN 1000® analyzer and manual slide morphological examination. The ADVIA 560 AL® showed acceptable accuracy in comparison with the Sysmex XN 1000® for FBC and DIFF parameters which is consistent with previously published studies investigating large bench-top Sysmex® and ADVIA analyzers [11]. The exception to this was the PLT and mean platelet volume (MPV) which were lower on the ADVIA 560 AL® versus the XN 1000®. This discrepancy has also been documented in a previous validation study involving multiple analyzers [12]. Impedance technology potentially underestimates platelet numbers and mean size, particularly in the presence of large platelets [13]. This recognized limitation has been addressed on the ADVIA 560 AL® with the platelet-red blood cell fragment differentiation morphology flag signaling the need for morphological examination. The outliers noted on the HGB correlation (Figure 1) comprised samples with very high white cell counts of > 70 x 10^9/L. The potential for increased turbidity in such samples resulting in a disturbance of the HGB measurement has been previ-

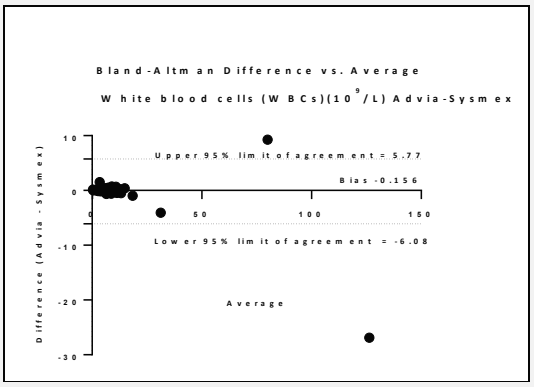
Hemoglobin (HGB) (g/dL)

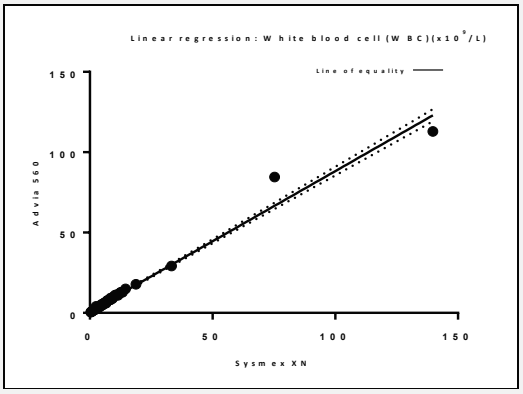




Test parameter	Correlation coefficient (r)	Bias		Slope (95% CI)	Intercept (95% CI)
		Mean	SD		
HB	0.9724	0.4372	0.46	0.920 (0.898 - 0.941)	1.341 (1.079 - 1.602)

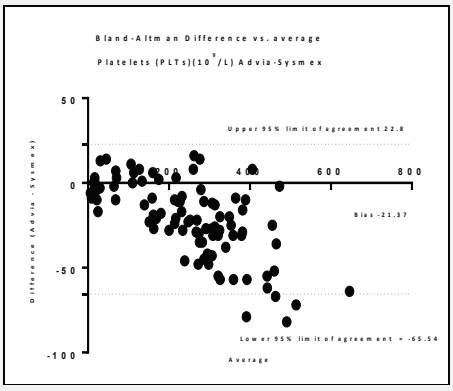
White blood cells (WBC) (x 10^9/L)

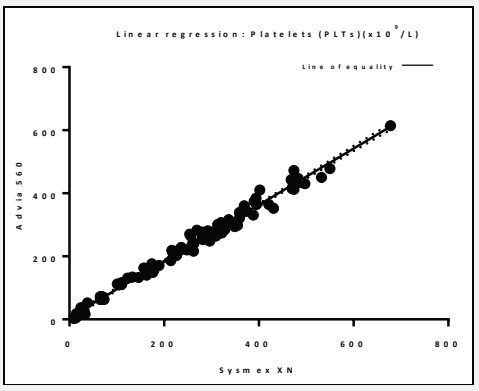




Test parameter	Correlation coefficient (r)	Bias		Slope (95% CI)	Intercept (95% CI)
		Mean	SD		
WBC	0.9761	-0.1566	3.02	1.08 (1.062 - 1.106)	-0.45 (-0.679 - -0.214)

Platelets (PLTs) (x 10^9/L)





Test parameter	Correlation coefficient (r)	Bias		Slope (95% CI)	Intercept (95% CI)
		Mean	SD		
PLT	0.9857	-21.37	22.54	0.91 (0.888 - 0.932)	2.9 (-3.4 - 9.3)

Figure 1. Bland Altman and linear regression analyses of white blood cells, hemoglobin, and platelets.

ously documented [14]. The ADVIA 5-part DIFF showed good correlation with the gold standard manual morphological slide examination with the exception of basophils, a finding which has also been documented in other evaluations of hematology analyzers [15].
The ADVIA 560 AL® showed acceptable imprecision for FBC and % DIFF. Manufacturer's imprecision limits were not available for absolute DIFF counts, and neutrophil, lymphocyte, and monocyte absolute counts did not meet SOTA criteria [9]. The false negative rate of morphology flags was < 5% when compared with manual morphology. Additionally, the ADVIA 560 AL® showed good linearity for high and low ranges and < 1% carryover which is comparable with other small benchtop hematology analyzers [16].
The study has a major limitation in that the ADVIA 560 AL® analyzer is incompatible with microtainer samples and verification of the pediatric Sarstedt Monovette® tubes was not performed. Additional evaluation of the accuracy of the automated flagging of samples which require morphologic examination is also required. The time to analysis of the samples was within 8 hours, in accordance with ICSH recommendations [5]. A shorter time to analysis was not possible as some samples were collected at a neighboring hospital.
In conclusion, the ADVIA 560 AL® analyzer is a small benchtop hematology analyzer suitable for acute care centers and satellite laboratories owing to its small footprint, high throughput, and reproducible and accurate analytical results. This analyzer can potentially assist with the triaging and appropriate escalation of the level of care of patients presenting for emergency care.

Data Availability Statement:
All study data will be made available on request.

Ethics Approval Statement:
The Human Research Ethics Committee (HREC) of the University of the Witwatersrand approved the study (Protocol M1911201). Individual patient consent was waived.

Source of Support:
The analyzer and reagents were sponsored by Siemens Healthineers®.

Declaration of Interest:
The authors declare no conflict of interest with regard to this verification study.

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