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RESEARCH ARTICLE

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Differences in erythrocyte sedimentation rates using a modified Westergren method and an alternate method

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Introduction: Worldwide laboratories have adopted the use of modified or alternate methods for measurement of the erythrocyte sedimentation rate (ESR). The iSED from Alcor Scientific is a novel, alternate ESR method based on photometric aggregometry which offers improved operator safety and reduced analysis time. This study evaluated the diagnostic utility of the iSED in a South African patient population with a range of inflammatory disorders.

Methods: We compared the iSED with the predicate modified Westergren method (StaRRsed, Mechatronics, Zwaag, the Netherlands) measured at 60 minutes. Analysis was performed on K_2EDTA samples at three ESR measurement ranges (<20, 20-80 and >80 mm/h) in 120 pediatric and adult inpatients and outpatients over a 2-week period. Precision, stability, and carryover were performed in accordance with the revised International Council for Standardisation in Haematology guidelines.

Results: The iSED demonstrated acceptable imprecision with minimal carryover (2.86%). The correlation coefficients at the 3 ESR measurement ranges were $r = 0.58$, $r = 0.71$, and $r = 0.56$, respectively. The y-intercepts were −10.74 (CI −29.17 to 7.69), −5.95 (CI −18.60 to 6.69) and 246.05 (CI 591.42-99.31). This indicated a difference of a constant nature with an overall mean difference of 7.99 mm/h (CI 5.87-10.13) ($P < 0.001$). iSED ESR measurements were stable up to 24 hours when stored at room temperature or at 4-8°C.

Conclusion: This study demonstrated differences in ESR results, predominantly at extremes of the analytical range, using an alternate method. Careful consideration and performance monitoring of these novel methods are advised.

KEYWORDS
alternate erythrocyte sedimentation rate measurement, EDTA tube, erythrocyte sedimentation rate, iSED, verification

1 | INTRODUCTION

The erythrocyte sedimentation rate (ESR) or length of sedimentation reaction of blood, first described over 120 years ago, is a widely used, non-specific screening test.[1,2] Although the test lacks specificity, the ESR is informative in a variety of inflammatory conditions, including rheumatoid arthritis, giant cell arteritis, polymyalgia rheumatica, and other connective tissue disorders.[3] In addition, the ESR is frequently requested by oncologists to monitor patients with Hodgkin Lymphoma post-chemotherapy for early disease relapse.[4] The ESR is usually performed in conjunction with more sensitive and specific tests for evaluating disease activity such as the C-reactive protein (CRP). The CRP, which increases within 4-6 hours of onset of inflammation or injury, is more useful for disease diagnosis. In contrast, the ESR which rises within 24-48 hours and declines slowly thereafter is more valuable for predicting a response to treatment and monitoring disease activity.[5,6]

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Westergren defined the reference method for ESR measurement, which uses a dilution of four volumes of blood to one volume of sodium citrate.[7] This measures the distance in millimeters (mm) that red blood cells (RBC) fall in a vertical column after 1 hour thereby measuring all three stages of RBC sedimentation. In the first stage, the RBC form rouleaux, in the second stage, settling of the aggregates occurs at a constant rate, and in the final stage, the rate of sedimentation slows as the aggregated RBC pack at the bottom of the tube. The end result is a compact column of sedimented RBC with a clear plasma portion. The traditional Westergren method has several well-described limitations for routine laboratory practice.[8] In order to address these, novel alternate and modified methods have been developed for ESR measurement. Alternate ESR methods employ different principles such as centrifugation or photometric aggregometry. These methods measure the initial stage of the ESR, namely rouleaux formation, which results in a significantly shorter analysis time. Furthermore, these methods offer technical innovations such as closed tube analysis with improved operator safety; use of ethylenediamine tetra-acetic acid (EDTA) tubes; reduced blood volume requirements and longer sample stability. Several studies of modified ESR methods have demonstrated improved precision and excellent correlation with the reference Westergren method.[9-11] However, variable results have been reported using alternative methods of ESR measurement in patients with a range of clinical disorders.[11-14] This raises the concern over introduction of a test principle that differs from the reference Westergren method.

The iSED (Alcor Scientific Inc, Rhode Island, USA) is a newly developed automated alternate ESR analyzer. Similar to other alternate ESR tests on the market, the iSED is a closed tube random-access analyzer which has been designed to improve the laboratory workflow by producing results within 20 seconds from EDTA tubes. This method is based on photometric aggregometry and requires a minimum sample volume of 100ul. This study aimed to verify the diagnostic and clinical utility of the iSED in accordance with the International Council for Standardisation in Haematology (ICSH) recommendations before accepting it into routine practice.[15]

2 | MATERIALS AND METHODS

2.1 | Study design

The iSED was verified with regards to precision, stability, carryover, and comparability to the reference StaRRsed (Mechatronics, Zwaag, the Netherlands) analyzer. The StaRRsed is a modified Westergren method which is currently used for measuring ESR at the Haematology Laboratory at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). This verification was performed in accordance with the revised ICSH2011 and 2017 and the Clinical and Laboratory Standards Institute (CLSI) (2011) recommendations.[15-17]

2.2 | Study protocol

2.2.1 | Blood sampling

Adult and pediatric samples with adequate volume (>4 mL) from inpatients and outpatients which covered ESR values in the analytical range of 2-120 mm/h were randomly selected in May 2018.[15] Samples were collected in K_2EDTA tubes or BD Microtainer MAP microtubes (Vacutainer, Becton Dickinson, UK). Samples were stored at room temperature (RT) and analyzed by a dedicated technologist within 4 hours of collection. Results which indicated analysis failure were excluded from the final analysis. Samples were collected anonymously, and no identifying information was recorded.

2.2.2 | Laboratory methods

The manufacturer was responsible for installation and training of the laboratory staff members on the instrument operation, quality control, and safety. Seditrol commercial controls (Alcor Scientific, Rhode Island, USA) used for the evaluation were supplied by the manufacturer. Maintenance procedures were performed daily as per the manufacturer's recommendations. According to the manufacturer's operator manual, K_2EDTA samples were inserted manually into the sample entry port. Twenty samples were loaded consecutively into the sample wheel. In the microflow cell, RBC aggregation is directly measured by an optical detector in 20 seconds.

On the StaRRsed, K_2EDTA samples are diluted with citrate in a ratio of 1:4. Samples are subsequently aspirated into vertical glass pipettes. ESR measurement is performed after 60 minutes by an optical sensor which measures the difference in absorbance between the RBC and plasma layers. Temperature correction is applied. The laboratory's analyzer is compliant with international proficiency testing program. Daily internal quality control was performed with normal and abnormal StaRRsed ESR controls (Mechatronics, Richmond, USA).

2.3 | Comparison study

For the method comparison study, samples were analyzed in parallel. The iSED analyzer's measurement range (1-130 mm/h) was established from the samples analyzed. The Bland-Altman difference plot was used to assess the absolute differences, and a Deming regression analysis was used to determine the degree of correlation between the iSED and StaRRsed analyzers. Correlation coefficients and biases for samples in the low (<20 mm/h), middle (20-80 mm/h), and upper third (>80 mm/h) of the analytical range were determined. Statistical significance was assumed to be $P < 0.05$.

2.4 | Precision

Between-run precision was performed with normal and abnormal controls which were analyzed three times a day for five consecutive days. Within-run precision was performed using normal and abnormal controls and three patient samples (in the low, middle, and upper third of the analytical range) analyzed ten times each during the same 8-hour period. The coefficient of variation (CV) was compared to the manufacturer's precision limits.

2.5 | Carryover

Using the Broughton formula, three consecutive analyses of a patient sample with high viscosity (H1, H2, and H3) were analyzed followed by three consecutive analyses of a patient sample with a low viscosity (L1, L2, and L3). Carryover was calculated from the formula: Carryover (%) = (L1-L3)/(H3-L3) × 100. Parametric paired *t* test was used to assess the observed differences.

2.6 | Sample stability

Stability analysis was performed on ten samples: five normal and five abnormal. Analysis was performed at time zero (or as close to zero as possible) on the iSED. The samples were then divided into aliquots and stored at RT and at 4-8°C. Subsequent testing was performed after 4, 8, 12 and 24 hours of storage. The results were compared using a parametric paired *t* test.

2.7 | Reference ranges

Reference intervals were verified using existing samples in accordance with the CLSI guidelines.[16]

2.8 | Ethics

This study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (M-180236).

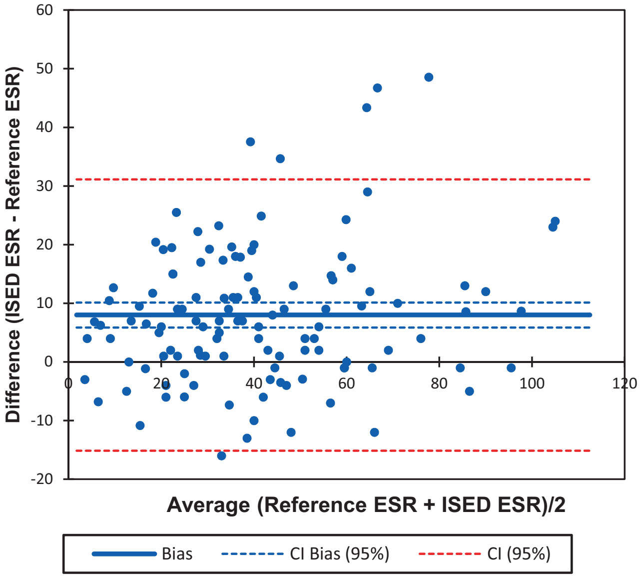

FIGURE 1 Bland–Altman difference plot comparing the iSED and the reference method

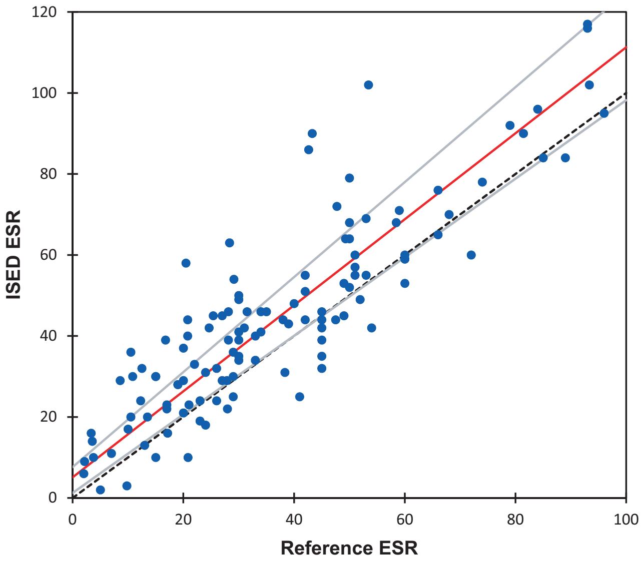

FIGURE 2 Correlation of the iSED and the reference method

3 | RESULTS

3.1 | Comparison study

One hundred and twenty samples (Female: Male of 5.4:1) were included in the final analysis with an age range of 6-85 years. The ESR requests were from the rheumatology/orthopedics outpatient department (51.4%), the emergency medicine department (37.1%), the infectious disease department (7.1%), and the oncology department (4.3%). The StaRRsed produced no results in 10 samples which were excluded from the final analysis. Of these, five were turbid samples (flagged as "hazy > 25 mm") and a further five were low-sample volumes. In addition, the StaRRsed flagged an additional 13 samples as unreliable owing to the presence of bubbles on sampling. The iSED produced no error readings or analysis failures during the study.

The analytical range of the iSED was 2-130 mm/h. The median (interquartile range) iSED ESR was 42.00 (29.00) mm/h which was significantly higher than the reference ESR value of 30.90 (20.69) mm/h ($P < 0.009$). ESR values on the StaRRsed were falsely increased in samples with low hematocrit levels (<0.36 L/L) and were adjusted for the patients' hematocrit results ($P = 0.316$).[18] The mean difference between the two methods was 7.99 mm/h (CI 5.87-10.13) (Figure 1). Deming regression analysis yielded a $r = 0.88$, y-intercept = 3.98 (CI 0.01-7.95) and slope = 1.11 (CI 0.99-1.22) (Figure 2). The majority of the data points were within the 95% limits of agreement with few outliers ($n = 6$). The outliers have been verified as true measurements performed within 4 hours of collection. The y-intercept of 3.98 (CI 0.01-7.95), however, indicated a significant difference of a constant nature between the two methods ($P < 0.001$).

We divided the results into subgroups according to the Westergren ESR levels. The results of the Deming regression and Bland-Altman analysis are shown in Table 1. Correlations in the

TABLE 1 Comparison statistics according to lower, middle, and upper third of the analytical range

Analytical range	N	Bias (95% CI)	Correlation coefficient (*r*)	Intercept	Slope
ESR (<20 mm/h)	26	1.79 (−1.76-5.35)	0.58	−10.74 (−29.17-7.69)	2.76 (1.22-4.29)
ESR (20-80 mm/h)	86	7.69 (4.95-10.44)	0.71	−5.95 (−18.60-6.69)	1.34 (0.99-1.69)
ESR (>80 mm/h)	8	8.66 (−0.42-17.73)	0.56	246.05 (591.42-99.31)	3.85 (0.09-7.60)

lower and upper third of the analytical range were weak to moderate with a difference of a constant nature ($r = 0.58$, $P < 0.001$ and $r = 0.56$, $P = 0.059$, respectively). The Bland–Altman difference plot showed a significant increase in the differences between the two tests at ESR values >80 mm/h with an observed mean difference of 8.66 mm/h (CI −0.42-17.73).

Using the StaRRsed as the reference, 103 (85.83%) ESR results from the iSED provided the correct clinical interpretation. However, there were 17 (14.17%) ESR measurements which would have resulted in a different clinical interpretation. Of these, 14 (11.67%) were false-positive results and 3 (2.50%) were false-negative results. Additional parameters were retrospectively retrieved from the laboratory information system in order to identify possible interfering variables, namely CRP, mean cell volume (MCV) and hematocrit. The mean hematocrit and MCV levels in the group which would have resulted in a different clinical interpretation were 0.39 ± 0.75 L/L and 90.69 ± 5.48, respectively. There was no statistically significant difference between the clinical groups ($P = 0.511$ and $P = 0.565$, respectively). In addition, the corresponding CRP levels did not differ significantly between the iSED and StaRRsed clinical groups ($P = 0.187$).

3.2 | Precision

The results of the within-run and between-run precision analysis on the iSED and StaRRsed with commercial controls are presented in Table 2. The within-run precision analysis for patient samples at low, middle, and high ESR levels was within the manufacturer's limits (Table 3).

3.3 | Stability

The undiluted ESR was stable for 24 hours on the iSED analyzer when stored at RT and at 4-8°C (Figure 3).

3.4 | Carryover

The percentage carryover for the iSED ESR measurement was 2.86%. This was not clinically significant and within the manufacturer's limit.

4 | DISCUSSION

Worldwide most laboratories have adopted modified or alternate ESR methods which offer improved operator safety and reduced analysis time.[15] This study evaluated the diagnostic utility of the iSED alternate ESR method compared to the StaRRsed in an adult and pediatric patient population with a range of inflammatory disorders. The iSED is a small bench-top device (36cmx27cmx34 cm) which has been developed for small to medium-sized laboratories. The pre-analytical steps of mixing are fully automated. In this study, the laboratory staff reported that the instrument was easy to operate following a short training period. Also, instrument maintenance was minimal and the iSED produced no error readings or analysis failures during the study. In contrast, the StaRRsed is a large analyzer (182 cm × 153 cm × 95 cm) which produces results in 60 minutes and thus places practical limitations on laboratory workflow. The StaRRsed reported 10 sampling errors and flagged 13 unreliable results in this study which may have resulted in incorrect clinical interpretation and management.

The ESR measurement on the iSED is a calculated ESR value in mm/h derived from the initial stage of the ESR, namely RBC aggregation during rouleaux formation. Complete sedimentation of the RBC aggregates is not measured. However, a significant mean difference of 7.99 mm/h (CI 5.87-10.13) ($P < 0.001$) between the iSED ESR and the StaRRsed ESR was observed in this study. On subgroup analysis, a poor correlation between the iSED and StaRRsed methods at ESR levels at the lower and upper third of the analytical range (2-130 mm/h) with a large mean bias of 1.79 mm/h (CI −1.76 to 5.35) and 8.66 mm/h (−0.42 to 17.73), respectively, were found.

This significant difference we observed in this study has also been observed in previous studies of the iSED.[3,12] These studies compared to methods using citrated whole-blood samples also reported a large positive bias, in particular at higher ESR levels. Westergren ESR testing methods are influenced by intrinsic factors such as hematocrit and viscosity as well as extrinsic factors such as sample length and temperature,[13] whereas these factors do not interfere significantly with ESR measurement on the iSED. Bogdaycioglu et al[12] found correlation of 0.76 with the manual Westergren method across all ranges with a mean bias of 13 mm/h (CI −35.7 to 61.6). Biederman et al[19] reported a mean bias of 6 ± 36 mm/h at ESR levels > 30 mm/h when compared to the Streck ESR Autoplus (Streck, Omaha, NE). However, across all ranges, the mean bias was small at −0.3 ± 12 mm/h.

Similarly other novel methods, have also been reported to overestimate the ESR compared to the reference Westergren method.[10,14,20] Results of proficiency testing indicate differences of ~40% between Westergren and non-Westergren-based methods in particular at upper and lower ends of the analytical range.[15] Shelat et al[14] studied a pediatric population and found a correlation 0.63 with a mean bias of 3.30 mm/h (CI 1.52-5.08) in the normal range 0-20 mm/h with the ESR STAT PLUS (HemaTechnologies, Lebanon, NJ). The results of this centrifugation

TABLE 2 Within-run and between-run precision analysis with commercial controls

	Mean ± SD (mm/h)	CV (%)	Expected range (mm/h)
Within-run precision			
Normal control			
iSed method	10.30 ± 1.34	12.99	3-17
StaRRsed method	4.70 ± 0.48	10.28	0-10
Abnormal control			
iSed method	62.40 ± 2.41	3.87	38-90
StaRRsed method	39.80 ± 0.42	1.06	33-53
Between-run precision			
Normal control			
iSed method	10.20 ± 1.32	12.9	3-17
StaRRsed method	4.60 ± 0.52	11.23	0-10
Abnormal control			
iSed method	62.67 ± 1.99	3.17	38-90
StaRRsed method	41.30 ± 1.42	3.43	33-53

TABLE 3 Within-run precision analysis on the iSED ESR analyzer with patient samples

	Normal	Abnormal-Middle range	Abnormal-High range
Measured mean (mm/h)	13.50	21.00	85.00
SD	2.07	2.67	7.44
CV (%)	15.33	12.72	8.75
Manufacturer's limits (%)	<20	<15	<10

method, however, are strongly influenced by extrinsic factors such as mixing. Mahlangu et al and Vennapusa et al showed a correlation of 0.96 and 0.83 with a mean bias of 6.6 mm/h (CI 5.0-8.1) and 7.13 mm/h, respectively, across all ranges on the Streck ESR Autoplus.[10,20] In contrast, other novel methods have been reported to underestimate the ESR, in particular at lower ESR levels.[11,13] Curvers et al[13] showed a correlation of 0.83 with a mean bias of −5.7 mm/h (CI −50.8 to 39.4) on the Ves-Matic Cube 200 (Diesse Diagnostica Senese, Siena, Italy), as compared to the Westergren method. Variable results, however, have been reported with this method, which measures all three stages of ESR sedimentation with an analogue sensor.[12,21] Further, this method has several limitations. These include a minimum sample volume of 4 mL, analysis time of 20 minutes and no automated dilution. As such hematocrit and viscosity will interfere significantly with results of this sedimentation method. The Test-1(Alifax S.p.A., Polverara, Italy), in contrast, performs the ESR from a small volume of undiluted blood in three minutes. A previous report by Van der Maas et al[11] however, showed a correlation of 0.67 with a mean bias of −4.4 mm/h (CI −7.8.4 to 1.0) as compared to the StaRRsed at 60 minutes. These studies confirm that systemic biases exist among automated testing devices based on aggregation or centrifugation principles as compared to sedimentation methods.

We considered additional potential factors that might be responsible for the observed systematic bias between the iSED and StaRRsed. The differences were not related to imprecision because the precision of the iSED was acceptable and did not differ significantly from measurements reported by the Westergren method.[10] The imprecision of the abnormal ESR control, which encompasses the clinically significant ESR range, was low. However, the imprecision of the normal ESR control was high. This, however, does not affect the clinical reliability of the measurements as it encompasses the ESR of the normal population.[22] Accordingly, the College of American Pathologists' proficiency testing scheme for 2017 reported a %CV of 17.4% for ESR results in the normal reference range on 310 iSED users. In this study, normal and abnormal patient samples were stable when analyzed on the iSED beyond 24 hours when stored at RT and 4-8°C, thus excluding instability as a potential factor. A major limitation of the Westergren ESR is the need to analyze the test within 4 hours from the time of collection when stored at RT.[15] The result is that many referred ESR samples in everyday practice are rejected. Alternate and modified ESR's performed in EDTA, however, have demonstrated improved sample stability.[12,21] Both test methods use EDTA as an anticoagulant; therefore, higher hematocrit values may have been a contributing factor. Our analysis showed that the StaRRsed had a tendency to overestimate the ESR in low hematocrit samples, whereas intrinsic factors did not interfere with ESR measurement on the iSED. This effect was reduced by applying the Fabry correction to the StaRRsed results.[18]

In order to determine the suitability of the iSED for this specific patient population, the clinical performance of this method was

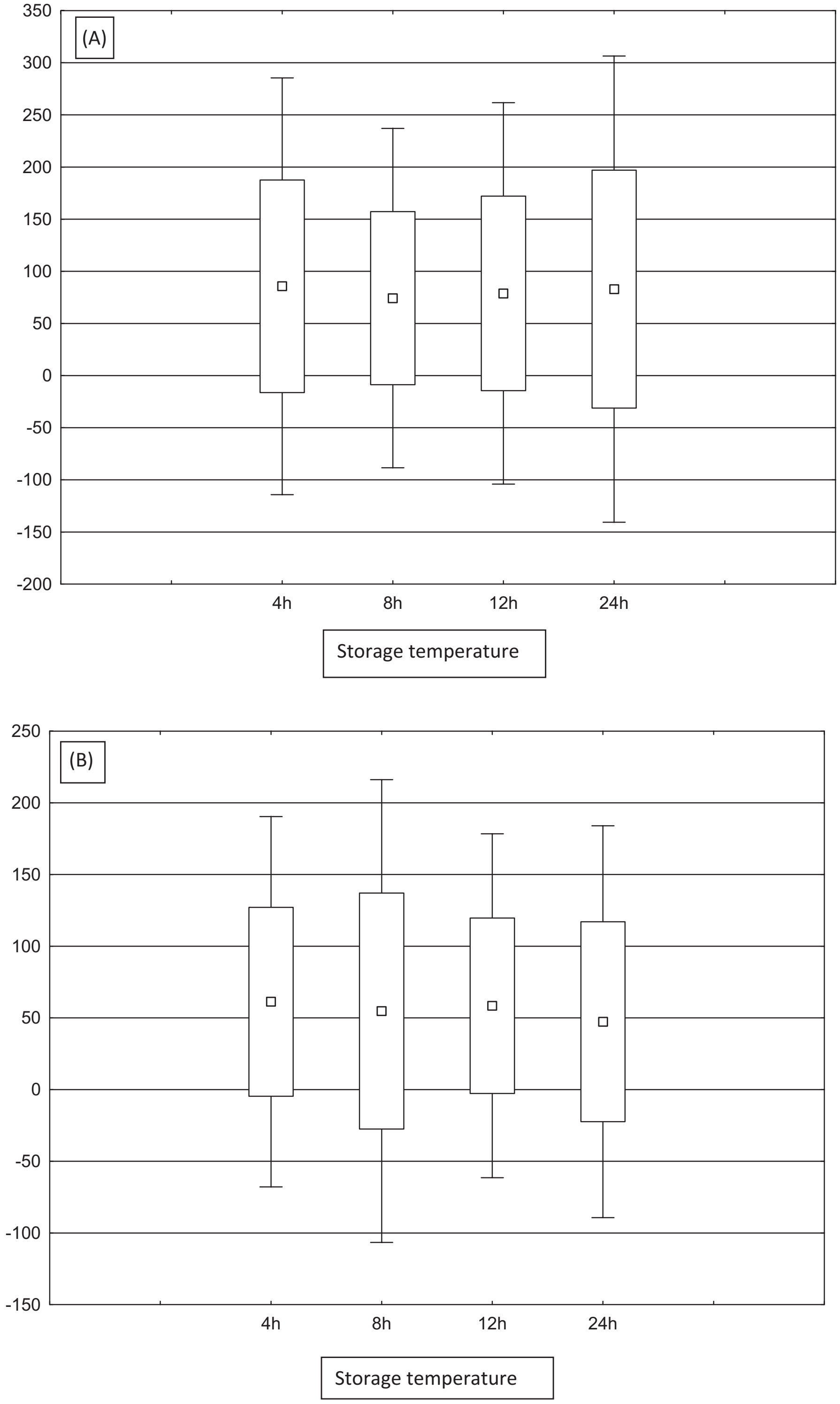

FIGURE 3 Boxplot of the mean percentage difference during storage at room temperature (A) and 4-8°C (B) for the iSED ESR measurement

assessed. There were 14 samples (11.67%) which would have resulted in a different clinical interpretation. On analysis of the corresponding CRP, hematocrit, and MCV levels, a significant difference was not observed. This raises concern that alternate and Westergren methods are not interchangeable. Fundamentally, the alternate and Westergren methods measure different analytical endpoints. Westergren methods measure erythrocyte sedimentation, whereas alternate methods measure erythrocyte aggregation. Real-time studies have demonstrated that alternate methods estimate the ESR from light reflected from or transmitted through a blood sample during initial rapid erythrocyte aggregation.[23] It follows that careful consideration and performance monitoring of these novel methods are advised.

In this study, the majority of the patients were rheumatology outpatients with rheumatoid arthritis. Van der Maas et al[11] previously demonstrated that use of an alternate ESR method affected the validity of the Disease Activity Score 28 (DAS 28). In their study of patients with rheumatoid arthritis, 26% of patients were misclassified when the Westergren ESR was replaced by the Alifax Roller Test-ITH ESR. As such, careful clinical and laboratory monitoring of these novel methods is indicated. In conjunction with the ICSH recommendation, we advise that the following interpretative comment be added to results from the iSED in order to assist clinicians with the correct interpretation: "This result was obtained with an ESR instrument that is not based on the standard Westergren methodology. The sensitivity and specificity of this alternate method for various disease states are 97.78% and 44.44%, respectively.[15]"

A limitation of this study is that samples with interfering substances such as fibrinogen and paraprotein, which increase rouleaux formation, were not collected during the study period. Additionally, the iSED was not compared with the manual Westergren method which is the gold standard. This study, however, contributes to the published literature as the manual Westergren method has largely been replaced worldwide by automated methods owing to the inherent limitations of the manual method.

5 | CONCLUSION

In conclusion, the iSED is a novel alternate method for ESR measurement which provides rapid and precise determination of the ESR. The analyzer offers major advantages including reliability, simplicity, use of EDTA samples with reduced sample volume and prolonged sample stability. This has the potential to reduce the sample rejection rate in routine clinical practice. This study confirmed differences in ESR results measured by the iSED as compared to the reference StaRRsed method. Difference was largely observed at the high and low ends of the analytical range. Careful consideration and performance monitoring of these novel methods are advised when used in routine laboratory practice. Further studies evaluating the impact of alternate ESR methods on clinical diagnosis and management are required.

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