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Analytical validation of the iSED automated analyzer for erythrocyte sedimentation rate

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Abstract

Introduction: iSED is an alternate automated analyzer for erythrocyte sedimentation rate (ESR) based on photometric rheology technology that estimates ESR by measuring rouleaux formation. The aim was to evaluate the analytical performance of the iSED analyzer and compare the results with the Westergren method and another alternate ESR analyzer, TEST1.

Methods: Validation was performed at two study sites according to the recommendations by the International Council for Standardization in Haematology and included determination of intrarun precision and inter-run precision, bias, carryover, and method comparison, which was further assessed for samples with normal and low hematocrit, as well as per low, middle, and upper third of the analytical range.

Results: Intrarun coefficients of variation (CVs) with commercial controls were 4.0% and 1.8%, while inter-run CVs 7.5% and 0.7%, for the normal and pathological range, respectively. Intrarun CVs obtained with patient samples were 19.9%, 9.9%, 10.3%, and 9.4%, the highest being for the lowest ESR value. Correlation coefficients for the comparison between iSED and Westergren were 0.862 (Site-1) and 0.916 (Site-2). While proportional difference with a positive bias was revealed at Site-1, comparison at Site-2 showed both constant and proportional difference and a negligible negative bias. Higher correlation was obtained for samples with low than normal hematocrit. Comparison between iSED and TEST1 yielded a correlation coefficient of 0.986, constant and proportional difference, and positive bias. Carryover was 3.2%.

Conclusion: This study proved the analytical validity of the iSED analyzer, despite minor discrepancies to the Westergren method that can be attributed to methodological differences.

KEYWORDS

automation, erythrocyte sedimentation rate, iSED, validation, Westergren method

1 | INTRODUCTION

The erythrocyte sedimentation rate (ESR) has a long-standing tradition in laboratory practice and is still one of the most commonly used laboratory tests.[1-4] ESR is a result of a complex physicochemical phenomenon that consists of aggregation of red blood cells (RBCs) and their grouping as rouleaux formations under the influence of acute-phase proteins, followed by their decantation and final aggregation.[5-7] Although it is traditionally considered a laboratory inflammation indicator, the process of erythrocyte sedimentation

is influenced by other numerous physiological and pathophysiological factors, most significant being anemia, alterations in RBC morphology, and presence of paraproteins, thus limiting its utility in inflammatory conditions.[5] With the introduction of more specific inflammatory biomarkers, its usefulness has decreased and nowadays ESR remains helpful in the diagnosis and monitoring of a limited number of clinical conditions, in particular rheumatoid diseases,[8] orthopedic infections,[9] and Hodgkin's lymphoma.[10]

The International Council for Standardization in Haematology (ICSH) defines the Westergren method originally introduced in 1921 as the gold standard method for ESR determination. The original Westergren method uses whole blood diluted with a liquid citrate anticoagulant (ratio 4:1) and measures the rate at which erythrocytes settle down in a vertically mounted tube in 1 hour.[11,12] In the last two decades, a number of novel semi-automated and automated methods for ESR measurement have been developed. According to the recent ICSH classification, these novel technologies are termed as modified Westergren methods when they presume minor modifications to the gold standard Westergren method, and alternate ESR methods for those based on diverse methodological principles.[11] These novel technologies measure distinct phases of the erythrocyte sedimentation process, and results obtained with different methods can differ.[2,11] In terms of standardization and to ensure ESR results comparability, ICSH published recommendations for objective assessment of ESR methods, defined that all new technologies and analyzers have to undergo a thorough validation process prior to introduction into routine practice and that only those that provide results comparable to the Westergren method with diluted blood in 1 hour or normalized to 1 hour are of clinical value.[11]

The aim of our study was to evaluate the analytical performance of the iSED automated analyzer (ALCOR Scientific Inc) that is classified as an alternate ESR method, and compare the results with the Westergren method and additionally, with another alternate ESR analyzer, TEST1 (Alifax Spa).

2 | MATERIALS AND METHODS

2.1 | Settings and study design

Validation of the iSED analyzer was performed at the Department of Laboratory Diagnostics, University Hospital Center Zagreb, Croatia (Site-1), in the period from July to September 2018 and the Department of Laboratory Medicine, University Hospital of Padova, Italy (Site-2), from June to July 2019. The part of the study performed at Site-1 included determination of intrarun and inter-run precision, estimation of bias, carryover assessment, and method comparison with the Westergren method. At Site-2, iSED results were compared with the Westergren method and additionally with the TEST1 analyzer. The analytical validation was entirely carried out on anonymized pre-existing samples with routinely requested ESR, once routine testing had been completed. All samples represent leftover material otherwise destined for discarding. This study was part of the standard validation procedure that is a requirement for accredited laboratories in compliance with the International Standard ISO 15189. The entire study was conducted in accordance with the principles of the Declaration of Helsinki and under the terms of all relevant local legislation.

2.2 | iSED analyzer

iSED is an automated analyzer that estimates ESR using the photometric rheology technology that measures the aggregation of RBCs in the phase of rouleaux formation. A volume of 100 µL of sample is aspirated directly from the ethylenediaminetetraacetic acid (EDTA) tube into a microflow cell where erythrocyte aggregation is measured using an optical detector. The rate of aggregation correlates with the sedimentation rate, and results are converted to Westergren units.[11,13] A maximum of 20 samples can be analyzed at a time, with the first result being available within 3 minutes, and a continuous release of the following results every 20 seconds.

2.3 | Manual Westergren method

At Site-1, ESR results measured by the Westergren method were obtained from routinely requested ESR since this method is used in everyday routine in the laboratory. Patient whole blood samples were drawn in 5-mL BD Vacutainer Seditainer tubes with blacktop (Becton Dickinson) that contains buffered sodium citrate (3.8%) as the anticoagulant. In this way, citrate diluted blood (four volumes of blood to one volume of citrate) is obtained. The samples were mixed 8-10 times by complete inversion prior to analysis and immediately put into the appropriate BD Seditainer stand (Becton Dickinson) in a vertical position.

At Site-2, EDTA samples were diluted manually with a trisodium citrate dihydrate solution (3.8%) in a ratio 4:1, mixed appropriately, immediately aspirated into circular glass Westergren tube with an inner diameter of 2.55 mm, and placed in a vertical position in a supporting rack.

ESR results were read after 1 hour by visual determination as the distance from the top of the plasma to the upper layer of RBCs and expressed in mm. All analyses were performed within 4 hours from venipuncture.

2.4 | TEST1 analyzer

TEST1 is an alternate automated ESR analyzer that utilizes capillary photometric-kinetic technology. Specifically, the analyzer pipettes 175 µL of EDTA-anticoagulated blood into a capillary where it is accelerated causing RBC aggregation that is measured photometrically. The obtained result is transformed to Westergren values. The first result is obtained within 5 minutes, with a subsequent release every 20 seconds.[11,14,15]

2.5 | Precision and estimation of bias

Intrarun precision and inter-run precision were determined by analyzing commercially available control samples SEDITROL® (ALCOR

Scientific Inc) composed of stabilized human blood, in the normal and pathological range. Control samples were analyzed one at a time three consecutive times for 5 days, following the procedure illustrated in the Clinical Laboratory Standards Institute (CLSI) EP15-A3 protocol.[16] Obtained results were evaluated with respect to manufacturer's claimed values. Additionally, intrarun precision was assessed by performing 10 replicate measurements of four routine patient samples with ESR values spanning through a wide ESR range.

Inter-run precision data were used for calculation of bias (%) using the following equation:

$$\text{Bias}\,(\%) = ((\text{Mean value} - \text{Target value})/\text{Target value}) \times 100.$$

2.6 | Method comparison

A total of 527 routine samples (222 female and 305 male; median age 59, ranging from 0 to 96) at Site-1 and 120 routine samples (39 female and 81 male; median age 67, ranging from 5 to 96) at Site-2 were used for method comparison. At Site-1, ESR on the iSED analyzer was measured from EDTA samples that were routinely sent for hematological analysis and had a paired citrate tube for ESR determination from the same venipuncture. At Site-2, the same undiluted EDTA sample was used for determination of ESR using iSED and TEST1, while for the Westergren method, the EDTA-anticoagulated sample was diluted manually with 3.8% citrate solution in a ratio 4:1, according to the ICSH recommendations.[11,12] All analyses were performed within 4 hours from sample collection. Statistical analysis was performed for all samples included in the method comparison study that covered the whole analytical range of the iSED analyzer (1-130 mm). The samples at Site-1 were further divided into groups according to the ESR values obtained with the Westergren method, that is, low (<40 mm), middle (41-80 mm), and upper third (>80 mm) of the analytical range. Additionally, results were compared for groups of samples with hematocrit values within and below the reference range. Hematocrit was determined as part of the complete blood count on Sysmex XN-10 automated hematology analyzer at Site-1 and Sysmex XE-2100 at Site-2, both produced by Sysmex Corporation, Kobe, Japan.

2.7 | Carryover assessment

Potential sample carryover was assessed according to the CLSI H26-A2 protocol,[17] that is, by analyzing 2 patient samples, one with high (H) and low (L) ESR values, in the following order: The sample with high ESR value was analyzed in triplicate followed by three analyses of the sample with low ESR value. Carryover was calculated as follows:

$$\text{Sample carryover}\,(\%) = ((L1 - L3)/(H3 - L3)) \times 100.$$

2.8 | Statistical analysis

For precision evaluation, mean values, coefficients of variation (CVs), and standard deviation (SD) were calculated. Data distribution normality was assessed with the Shapiro-Wilk test. For all assessed comparisons, non-parametric Spearman's rank correlation coefficient (ρ) was determined. Passing-Bablok linear regression analysis and Bland-Altman analysis were performed to test result comparability, that is, to estimate constant and/or proportional difference, bias, and limits of agreement. All statistical analysis was carried out using the MedCalc statistical software for Windows, version 14.12.0 (MedCalc).

3 | RESULTS

The results of precision study and estimation of bias with commercial control samples are presented in Table 1.

Four patient samples analyzed in 10 replicates yielded mean values ± SD of 3 ± 1, 23 ± 2, 53 ± 5, and 78 ± 7 mm, with the following intrarun CVs 19.9%, 9.9%, 10.3%, and 9.4%, respectively.

The median ESR value for 527 samples measured with the iSED analyzer at Site-1 was 14 mm (interquartile range (IQR): 6-29) and 20 mm (IQR: 10-41) determined with the Westergren method. The obtained Spearman's rank correlation coefficients (ρ) were 0.862 (95% CI: 0.838-0.882). Passing-Bablok linear regression revealed proportional difference, with a regression equation $y = -0.16 + 0.73x$ (Figure 1A), while Bland-Altman analysis showed a positive bias of 8.1 (95% CI: 7.0-9.3) (Figure 1B).

The comparison at Site-2 yielded median ESR values of 32 mm (IQR: 16-59) obtained with iSED, 25 mm (IQR: 10-61) with the Westergren method and 35 mm (IQR: 12-80) with the TEST1 analyzer. For the comparison between iSED and the Westergren method, Spearman's ρ was 0.916 (95% CI: 0.882-0.941). Constant

TABLE 1 Precision and bias obtained by analyzing commercial control samples Seditrol® in the normal (Level 1) and pathological range (Level 2) for five consecutive days in triplicate

	Intrarun precision		Inter-run precision		
	Mean ± SD	CV (%)	Mean ± SD	CV (%)	Bias (%)
Seditrol® Level 1 lot C128 (10 ± 7 mm)	13 ± 1	4.0	13 ± 1	7.5	30
Seditrol® Level 2 lot C228 (64 ± 26 mm)	64 ± 1	1.8	64 ± 1	0.7	0

Abbreviations: CV, coefficient of variation; SD, standard deviation.

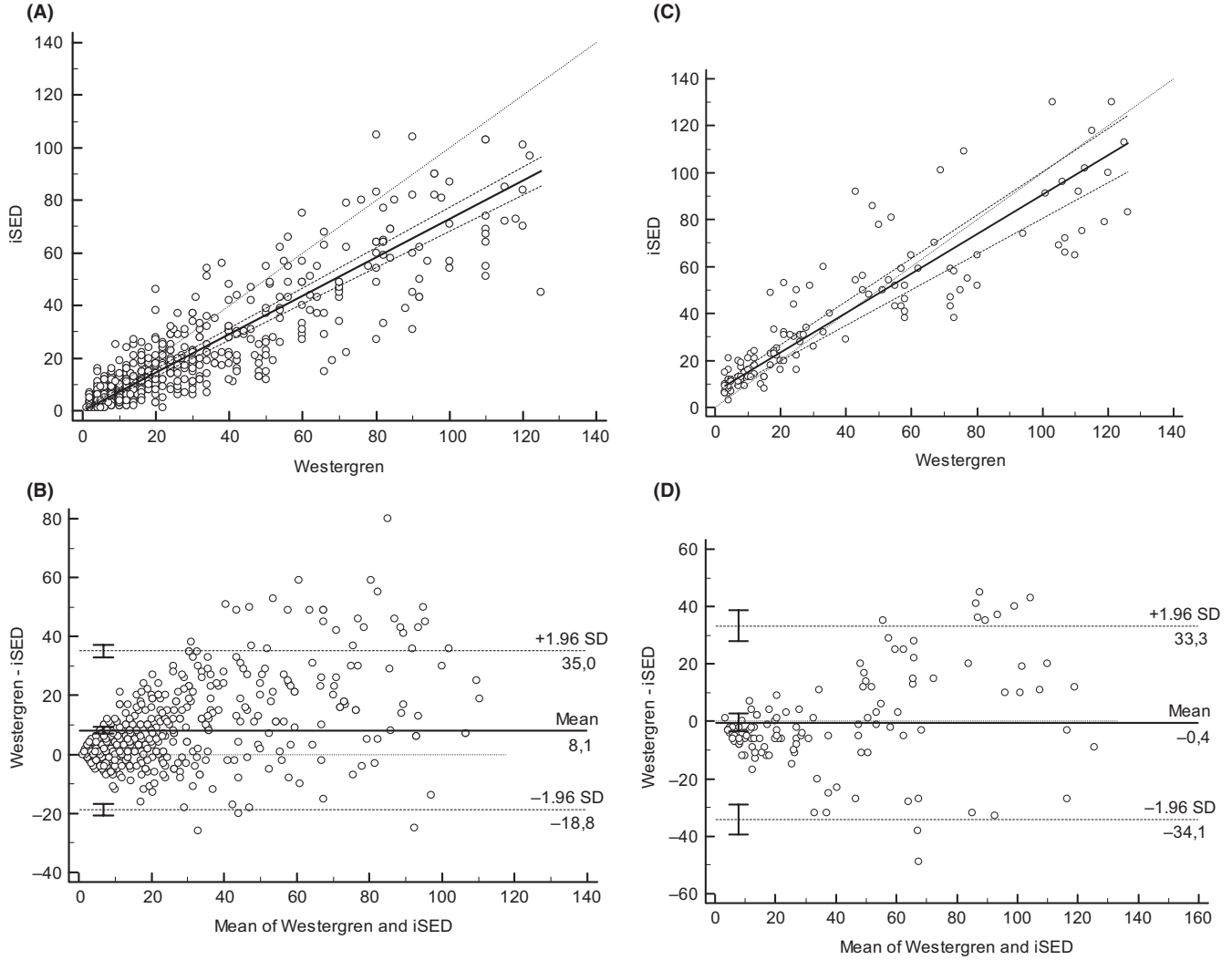

FIGURE 1 Comparison between iSED and the Westergren method at Site-1 (N=527): (A) Passing-Bablok scatter diagram with an equation $y = -0.16 + 0.73x$, intercept −0.16 (95% CI: −0.61 to 0.63) and slope 0.73 (95% CI: 0.69 to 0.77); (B) Bland-Altman scatter diagram with a mean bias 8.1 (95% CI: 7.0 to 9.3); Comparison between iSED and the Westergren method at Site-2 (N = 120): (C) Passing-Bablok scatter diagram with an equation $y = 6.64 + 0.84x$, intercept 6.64 (95% CI: 4.58 to 8.17) and slope 0.84 (95% CI: 0.76 to 0.92); (D) Bland-Altman scatter diagram with a mean bias −0.4 (95% CI: −3.6 to 2.7)

and proportional difference were observed, with an equation $y = 6.64 + 0.84x$ (Figure 1C) and a negligible negative bias of −0.4 (95% CI: −3.6 to 2.7) (Figure 1D).

Comparison between iSED and TEST1 yielded a correlation coefficient of 0.986 (95% CI: 0.979-0.990), while Passing-Bablok analysis revealed constant and proportional difference with an equation $y = 5.77 + 0.69x$ (Figure 2A). A positive mean bias of 7.9 (95% CI: 5.4-10.3) was obtained with Bland-Altman analysis (Figure 2B).

The results of comparison between samples subdivided into groups of low (<40 mm), middle (41-80 mm), and high (>80 mm) ESR values are presented in Table 2.

Table 3 shows the results of comparison of samples grouped according to hematocrit values.

The assessment of sample carryover yielded a potential contamination of 3.2%.

4 | DISCUSSION

This study shows that iSED presents with satisfactory precision characteristics and comparability with the gold standard Westergren method. However, it once again highlights that, despite obvious improvements in standardization of ESR methods, differences in ESR results can still be observed between methods that measure different phases of the RBC sedimentation process.

Hereby, we demonstrated a much better precision of iSED with commercial control samples at both evaluated levels than in a previously published study,[18] while patient samples yielded intrarun CVs similar to already reported data for iSED, with decreasing precision at medium and low ESR levels[13,18] This is in concordance with data from a lot of validation studies of automated ESR analyzers, regardless of the analyzer type and measurement principle[7,15,19-21] and can be attributed to small numbers rather

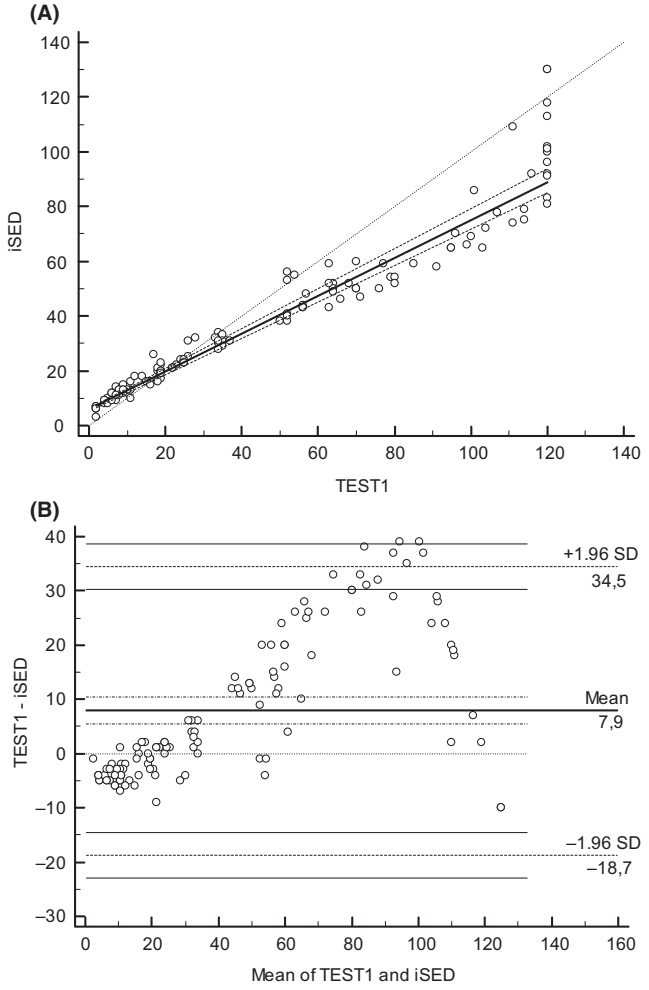

FIGURE 2 Comparison between iSED and TEST1 analyzer (N = 120): A, Passing-Bablok scatter diagram with an equation $y = 5.77 + 0.69x$, intercept 5.77 (95% CI: 5.1-6.33) and slope 0.69 (95% CI: 0.67-0.73); B, Bland-Altman scatter diagram with a mean bias 7.9 (95% CI: 5.4-10.3)

than poor analytical performance, therefore not being considered clinically significant.

The 30% bias obtained for the normal level equally does not affect the clinical reliability of results and cannot be attributed to analytical drawbacks of the iSED analyzer. As iSED pipettes a higher volume of control sample in the normal than in the pathological range, there was not enough sample volume for conducting the whole precision study from a single control tube, and on the fifth day, we had to start using a newly opened control tube of the same lot which probably caused a more random variation in results and, due to small numbers, yielded the respective bias.

The comparison between iSED and the Westergren method revealed higher correlation coefficients than in a previous validation study.[13] However, despite overall high correlations at both study sites, the disagreement and dispersion of results was frequently significant, especially at high ESR levels, meaning that a patient could have high ESR by Westergren and normal ESR measured with iSED, or vice versa, which could potentially lead to different clinical interpretation. These discrepancies can be attributed to methodological differences and different ESR measurement time points, as iSED estimates ESR by kinetic measurement of rouleaux formation in the initial sedimentation phase, in contrast to the original Westergren method that measures ESR after all three phases of the sedimentation. Moreover, ESR is not a well-defined analyte but rather reflects a physicochemical phenomenon that is susceptible to several underlying factors that can differently affect each particular ESR method. Interestingly, this was evidenced even in the comparison between iSED and TEST1, where results were strongly aligned, with a high correlation coefficient, but still both constant and proportional difference and a statistically significant positive bias were obtained, implying that differences can be occasionally observed even between ESR analyzers based on the same methodological principle.

Low hematocrit values are known to cause overestimation of ESR values determined with the Westergren method.[5] However, methods based on kinetic measurement, such as the ones incorporated in the iSED and TEST1 analyzer, should be less influenced by hematocrit as they estimate ESR by measuring the extent of rouleaux formation that is dependent on the presence of negatively charged plasma proteins, mainly fibrinogen and globulins. Unexpectedly, this was not proven in our study as comparison between iSED and Westergren of samples with low hematocrit displayed higher correlation than comparison of samples with normal hematocrit, indicating that hematocrit might not be considered a crucial influencing contributor to the differences between these two particular methods.

Moreover, the potential sample carryover of 3.2% obtained in our study is similar to the one (2.9%) reported in the study by Schapkaitz et al[18] but as it does not exceed the highest CV from precision study, it cannot be considered significant and can be attributed to analytical variation rather than actual sample contamination from previous analysis.

TABLE 2 Results of method comparison between iSED analyzer and the Westergren method at Site-1, divided per low, medium, and upper third of the ESR analytical range

	N	ρ	Intercept (95% CI)	Slope (95% CI)	Mean bias (95% CI)
Low third (<40 mm)	383	0.720	−0.7 (−2.0 to −0.1)	0.9 (0.8 to 1.0)	3.0 (2.3 to 3.8)
Medium third (40-80 mm)	91	0.528	−53.1 (−81.6 to −36.0)	1.7 (1.4 to 2.2)	17.7 (14.8 to 20.5)
Upper third (>80 mm)	53	0.297	−89.8 (−193.0 to −43.3)	1.7 (1.2 to 2.8)	28.4 (22.8 to 34.0)

Abbreviations: CI, confidence interval; ρ, Spearman's rank correlation coefficient.

TABLE 3 Results of ESR comparison between iSED and the Westergren method for samples with normal and low hematocrit values

		N	ρ	Intercept (95% CI)	Slope (95% CI)	Mean bias (95% CI)
Normal hematocrit	Site-1	320	0.817	0.3 (−0.5 to 0.9)	0.8 (0.7 to 0.9)	4.6 (3.4 to 5.7)
	Site-2	37	0.804	2.6 (−0.1 to 6.0)	1.4 (1.0 to 1.9)	−8.3 (−11.6 to −4.9)
Low hematocrit	Site-1	207	0.889	−2.4 (−3.6 to −0.6)	0.7 (0.7 to 0.8)	13.3 (11.1 to 15.5)
	Site-2	83	0.879	6.7 (3.5 to 10.7)	0.8 (0.7 to 0.9)	2.7 (−1.4 to 6.8)

Abbreviations: CI, confidence interval; ρ, Spearman's rank correlation coefficient.

This study has some limitations. Firstly, we did not assess sample stability. However, we strictly followed the manufacturer's recommendation that the samples should be analyzed within 4 hours from sampling, although the results of a recent study[18] regarding sample stability on the iSED analyzer showed much longer stability, that is, for 24 hours, either stored at room temperature or refrigerated at +4°C. Secondly, among possible interferences, only the effect of hematocrit has been assessed. Also, we are not aware whether any of the discrepancies observed can be attributed to underlying patients' pathophysiological conditions. Still, we believe that, in the era of increased implementation of automated ESR systems, our study can be useful as a starting point for laboratory professionals that are willing to transit to the use of alternate ESR analyzers. Automation of ESR analysis is being attractive as it poses many advantages in comparison with the Westergren method, including analysis from the EDTA sample, easier manipulation and enhanced personnel safety, higher reproducibility of results, and availability of quality control.[3,11,15,22]

As evidenced in this study, iSED analyzer provides accurate ESR measurement and acceptable concordance with the gold standard Westergren method, with minor discrepancies and occasionally limited agreement that can be attributed to different methodological principles. However, as ESR could be considered more a generic sign of pathophysiological alterations than a true laboratory measure, not particularly dense of specific clinical significance, for this target, iSED could provide acceptable discriminatory performance. Considering also the rapid measuring time and the easy-to-use interface, iSED seems suitable to be used in routine practice. Still, the differences observed remain a major issue and once again address the need for further efforts to provide harmonization between different available ESR analyzers and the Westergren method. Therefore, it is of upmost importance to assess analytical features of all novel ESR methods according to the ICSH recommendations,[11] to understand the methodological principles that can yield result discrepancies, in order to familiarize both laboratory and clinical staff to the use of new measurement techniques and in that way most efficiently serve the clinical needs.

CONFLICT OF INTEREST

None to declare.

AUTHOR CONTRIBUTIONS

IL, MM, EP, RZ, DR, and MP conceived and designed the study. IL, MM, FT, and EP performed laboratory measurements, analyzed, and interpreted the data. IL wrote the manuscript. MM, FT, and EP co-wrote the manuscript. RZ, DR, and MP revised the manuscript critically. All authors approved the final version of the article for submission.

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