



Research article

Blood-gas vs. Central-Laboratory analyzers: interchangeability and reference intervals for sodium, potassium, glucose, lactate and hemoglobin

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ABSTRACT

Background: Blood-Gas Analyzers (BGAs) are commonly used in parallel with central laboratory analyzers (CLAs). Given the often-divergent results between BGAs and CLAs this study aims to: 1. Determine whether the measurements of potassium (K), sodium (Na), glucose (Glu), lactate (Lact) and total hemoglobin (ctHb) on BGAs and CLAs are interchangeable; 2. Establish reference intervals (RIs) for both analyzer systems using an indirect statistical approach.

Methods: During a one-year study period K, Na, Glu, Lact and ctHb measurements from 500 arterial blood samples, measured on ABL 90 FLEX BGAs were compared with corresponding venous samples measured on Roche c8000 and Sysmex XN-9000 analyzers. Interchangeability of methods was tested based on the Acceptable Change Limit, Total Change Limit and the guidelines published by the German Medical Association for quality assurance in medical laboratories criteria. Indirect RIs were estimated based on all routine analysis data using the software Reference Limit Estimator (RLE).

Results: With the exception of Na, the BGAs differed significantly from the CLAs for the tested analytes ($P < 0.001$) but, with the exception of ctHb, did meet the interchangeability criteria. For K, Na, Gluc and ctHb the reference intervals obtained with RLE did not differ statistically between the analyzer systems.

Conclusion: The interchangeability criteria were met for Na, K and Gluc and Lact. The indirect RIs obtained with RLE, are comparable between two systems for Na, K, Gluc and ctHb. Lact differed significantly in the lower reference limit between the BGAs and CLAs. The simultaneous use of both analyzing systems is thus only advisable for Na, K and Gluc.

1. Introduction

For optimal clinical decision-making, it is important that laboratory results are available as soon as possible, especially for the detection and monitoring of life-threatening conditions in critically ill patients [1]. One way to achieve the rapid availability of laboratory results is via point-of-care testing (POCT) devices like blood gas analyzers. Blood gas analyzers (BGA), as the name implies, measure blood gases, but also electrolytes and metabolites like glucose and lactate, with the addition of total hemoglobin or hematocrit, providing crucial information to clinicians in the diagnosis of a variety of metabolic and respiratory disorders to expedite diagnosis and subsequent treatment of emergency conditions [2, 3, 4, 5]. The introduction of POCT led to the decentralization of laboratory tests [6]. Consequently, patient samples are often measured

with different analytical methods, using different types of equipment and clinicians often use the reported results interchangeably, unaware of the potential pitfalls.

Immediately connected to the problem of potentially divergent results and systemic bias from different analyzer systems is the question of appropriate reference intervals (RIs) for a given test and analyzer system. Reference intervals need to be clearly defined based on current best practice and, in case of point of care testing, based on the particular characteristics of POCT devices. The common and recommended protocol (the so-called “direct method”) for establishing RIs is to perform a RI study, where a limited number, usually at least 120 per sub-group, of healthy persons are tested to establish an RI based on the distribution of a given parameter among them [7]. An alternative approach (“indirect method”) uses large data sets of clinical laboratory results extracted from

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data bases of routine diagnostics and is based on a mixed population of diseased and supposedly healthy subjects. These large clinical data sets are subsequently used to infer the distribution of analyte values for healthy individuals to statistically derive reference intervals [8]. Since any systemic measurement difference between analyzer systems like POCT and CLAs could potentially result in shifts in the RIs, the task of implementing appropriate RIs in a given hospital becomes more complicated and potentially more confusing for the clinician, when confronted with more than one RI for the same analyte.

Based on the above-described fields of conflict, our study aims to tackle some of the problems resulting from operating POCT and central laboratory analyzers in parallel. As POCT models system, we used BGAs and compare them to their corresponding clinical chemical and hematological central laboratory platforms. First, we determined whether BGA and central laboratory analysis of sodium (Na), potassium (K), glucose (Gluc), lactate (Lact) and total hemoglobin (ctHb) are in fact equivalent and interchangeable with respect to their measured patient results. We conducted this study retrospectively, retrieving patient results from the laboratory information system, allowing for a conveniently large number of paired BGA and central laboratory samples, reflecting realistic, clinical field conditions. Second, we established and compared RIs for the aforementioned analytes for both analyzer systems using an indirect statistical approach based on a large clinical data set, again retrieved retrospectively from the laboratory information system.

2. Materials and methods

2.1. Data collection and study design

Over a one-year study period (September 2017 to September 2018), analyte concentrations for Na, K, Gluc, Lact and ctHb were retrieved retrospectively from the laboratory information system (LIS) database of the central laboratory of the University Clinic Halle (UKH). The LIS database includes both all BGA results of the UKH as well as the results of the analyzers of the central laboratory itself. Results for the aforementioned analytes were collected for arterial blood samples measured on ABL 90 FLEX BGAs, where corresponding venous samples measured on Roche c8000 and Sysmex XN-9000 analyzers in the central laboratory within a 30-minute time window. In cases of multiple BGA analyses within 30 min of a central laboratory sample, we chose the BGA specimen taken at the time closest to the central laboratory result for the method comparison study. We aimed at obtaining a sample size of 500 pairs per analyte for comparing the two different analyzer systems. In case of significant bias between the BGA and CLA results, the acceptable analytical deviation, or interchangeability, was evaluated based on the following three concepts: 1. Acceptable Change Limit (ACL) [9]; 2. Total Change Limit (TCL) [10]; 3. The guidelines published by the German Medical Association for quality assurance in medical laboratories (RiLiBÄK) [11].

For the establishment of indirect RI, we additionally retrieved all Na, K, Gluc, Lact and ctHb results for both BGAs and CLAs for the above-mentioned one-year period, irrespective of any pairing of results. Data sets were curated to only contain one data point per patient, to avoid artificial bias of the data. Each of the obtained datasets for a given analyte and analyzer type was then used to indirectly estimate the respective RIs with the software Reference Limit Estimator (RLI).

All data in this study were obtained from retrospective analysis of medical laboratory databases and the study was reviewed and approved by the ethics committee of the Medical Faculty of the Martin-Luther-University Halle-Wittenberg (approval 2018-176).

2.2. Blood sampling

Arterial blood gas samples were collected with heparinized safePICO syringes (1.7 mL, Radiometer Medical ApS, Denmark) and analyzed immediately on ABL FLEX 90 Plus analyzers (Radiometer Medical ApS,

Brønshøj, Denmark). Venous samples for laboratory analyses were collected in S-Monovette® Li-Heparin-Gel (4.9 mL, Sarstedt, Nümbrecht, Germany) and S-Monovette® K₂EDTA (2.6 mL, Sarstedt, Nümbrecht, Germany) and analyzed using Roche c8000 (Roche Diagnostics, Rotkreuz, Switzerland) and Sysmex XN-9000 (Sysmex Corporation, Kobe, Japan) analyzers in the central laboratory of the UKH.

2.3. Central laboratory measurements

Biochemical parameters were determined using Roche cobas 8000 modular analyzers of the central laboratory of the UKH, the ISE unit for electrolytes and the cobas c701 chemistry module for metabolites (Roche Diagnostics, Rotkreuz, Switzerland). Electrolytes were measured using an indirect ISE method, glucose was determined based on a UV-enzymatic method with hexokinase and lactate was measured by an enzymatic lactate oxidase assay. All analytes were measured using the commercially available Roche reagents. Total hemoglobin was determined with a Sysmex XN-9000 analyzer (Sysmex Corporation, Kobe, Japan) by photometry at 555 nm wavelength using the cyan-methemoglobin method. This method uses cyanide-free sodium lauryl sulphate as reagents. The Roche cobas 8000 modular platform, the Sysmex XN-9000 analyzer, and all their components were operated according to the manufacturer's instructions and manuals, with routine maintenance and quality control procedures.

2.4. POCT measurements

Nineteen ABL FLEX 90 Plus blood gas analyzers (Radiometer Medical ApS, Brønshøj, Denmark) are in use in the intensive care and emergency units of the UKH. All of the ABL FLEX 90 Plus analyzers are operated by trained and educated nursing staff under supervision of the central laboratory. The ABL FLEX 90 Plus blood gas analyzer utilizes potentiometry for the measurement of Na, K and Cl, amperometry for the measurement of Glu and Lact and spectrophotometry to measure ctHb.

2.5. Statistical analysis

Method comparison between POCT and central laboratory analyzers was performed using the statistical software Analyse-it for Microsoft Excel 5.4 (Analyse-it Software, Ltd., Leeds, United Kingdom). We used Bland-Altman plots and Passing Bablok regressions for gauging of differences and calculated the average bias (difference) and its statistical significance, as well as the 95% limits of agreement (LoA) according to the CLSI EP09 A3 guideline [12].

Since statistically significant biases between two methods can be of no, or only marginal, clinical significance, we tested the acceptable clinical interchangeability applying the ACL, TCL and RiLiBÄK criteria. We considered these three approaches because the first one (ACL) is solely based on analytical imprecision (CV_a), using the formula $ACL = 2.77 CV_a$. The factor 2.77 is derived from $Z\sqrt{2}$, where $Z = 1.96$, as determined by the 95% of confidence interval value for bi-directional changes. The second approach (TCL) takes into account the acceptable imprecision based on intra individual biological variation, using the formula $TCL = \sqrt{(2.77 CV_a)^2 + (0.5 CV_b)^2}$. Finally, the third approach is the guideline, which defines the basic requirements for quality management and quality assurance of laboratory medical examinations in medicine in Germany (RiLiBÄK). Blood gas analyzers and CLA methods were deemed interchangeable, if their calculated average bias was below at least two of the above-mentioned interchangeability criteria.

We estimated indirect RIs using the software Reference Limit Estimator (RLE) - version 20180511 (RLE49) (German Society for Clinical Chemistry and Laboratory Medicine, Germany). The RLE is based on large data sets (>5000 samples) of both supposedly healthy and diseased individuals to estimate the reference intervals of a given population and analyte. The statistical approach of RLE is to use a smoothed kernel

function for the distribution of the data, where the central part of the distribution represents the healthy population, which is used to estimate the Gauss distribution of the non-pathological values [8].

3. Results

3.1. Method comparison

Based on the 500 sample pairs for each analyte, the Passing-Bablok regressions of the method comparison BGA vs. CLA for Na, K, Gluc, Lac and ctHb are given in Figure 1. As can be seen from Figure 1, the Passing-Bablok regressions for all analytes represent good to excellent fits. The intercepts of the regression equations are all close to zero, ranging from -0.11 for Gluc and Lact to a perfect 0 for Na. The slopes are all close to one, ranging from 0.95 for Gluc to 1.03 for ctHb, with perfect slopes of 1 for Na and K. The Bland-Altman blots of the method-comparison are given in Figure 2 and a summary of median values, absolute and relative bias, the statistical significance and their associated 95% limits of agreement are given in Table 1. As can be seen from the Bland-Altman Blots, Na has the smallest bias by far, which is also statistically indistinguishable from zero, with a narrow LoA of -2.7%–2.8%. All other analytes have statistically significant biases, ranging from -2.6% for K up to 8.8% for Lact, which also has the largest LoA of -54,6% to 37,6%.

3.2. Interchangeability criteria

The details of the interchangeability criteria of ACL, TCL and RiliBÄK are given in Table 1. Irrespective of the analyte, ACL always gave the lowest threshold and the RiliBÄK criteria the highest threshold by far, being 4.5 times as high as the ACL criteria in case of Gluc. For three analytes, Na, K and Gluc, the estimated bias from the method comparison

was lower than all three criteria, for Lact the bias was still lower than the TCL and RiliBÄK, while for ctHb the estimated bias of 3.5% surpassed both ACL and TCL criteria, only being below the RiliBÄK threshold of 6%. As such, our results showed that only ctHb did not meet our predefined threshold for the acceptance criteria.

3.3. Indirect reference intervals

The indirect RIs estimated via the RLE for the Na, K, Gluc, Lact, and ctHb on both the BGA and the CLAs are given in Table 2. For Na, K, Gluc, and ctHb the estimated reference intervals are similar for the BGA and CLA and cannot be statistically distinguished, as indicated by their overlapping 95% confidence intervals for the lower (LRI) and upper reference interval (URI). For Lact, the LRI 95% confidence interval did not overlap, indicating that the reference interval differs significantly for the BGA and the CLA. Because of the strongly skewed distribution of the lactate values in the high concentration range, it was not possible to estimate a reliable URI for Lact.

4. Discussion

Comparison of test results, measured by multiple methods and different types of equipment, and their reliable use in patient support is of paramount importance. The use of multiple analyzers may lead to statistically or even clinically significant differences between values obtained by different instruments. In this study, we evaluated the interchangeability of the ABL FLEX 90 Plus BGA with the CLA platforms Roche Cobas c701 and Sysmex XN-9000 for Na, K, Gluc, Lact and ctHb. To do so, we used a retrospective method comparison, based on clinical data retrieved from the laboratory information system of the central laboratory of the UKH, which allowed for a conveniently large sample

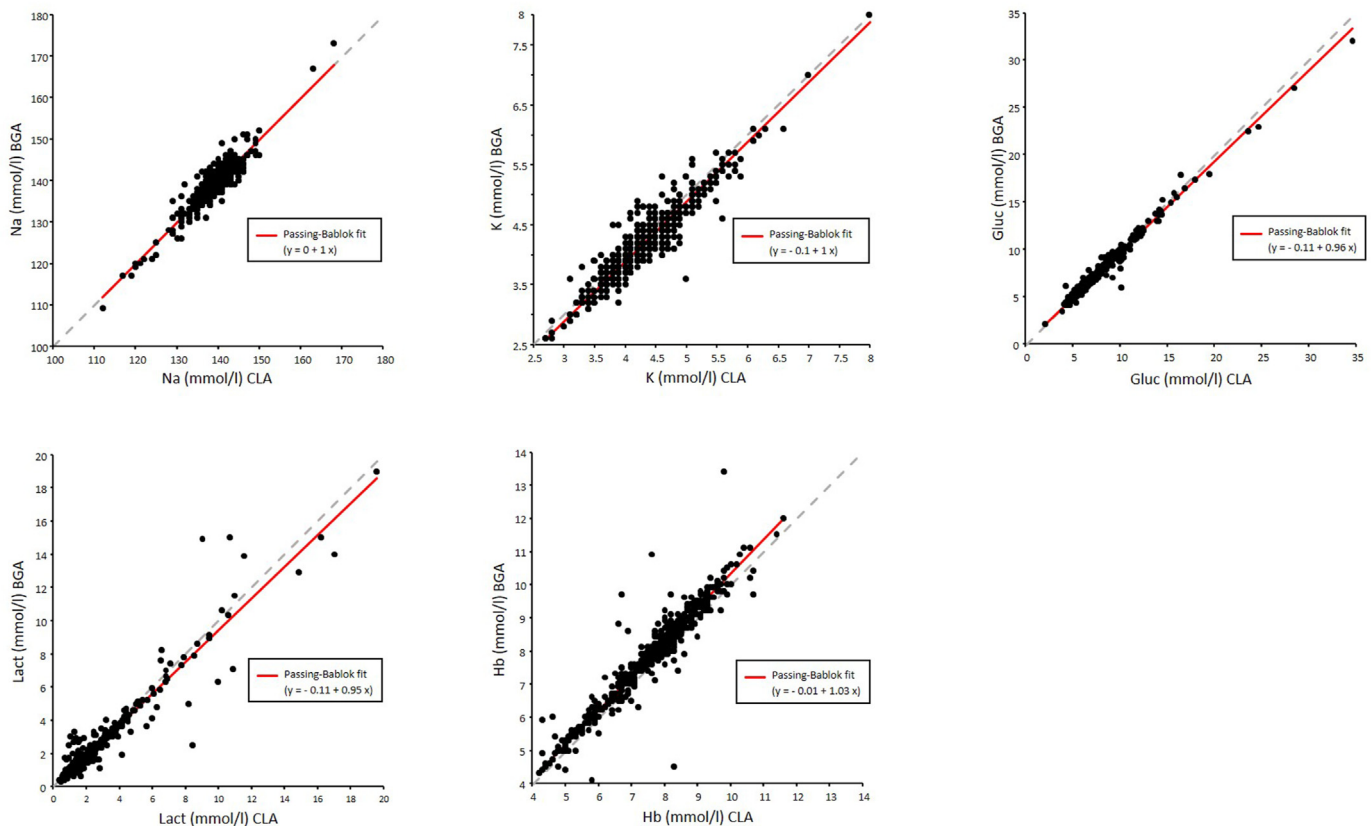


Figure 1. Passing-Bablok regression for the method comparison the ABL FLEX 90 Plus Blood gas Analyzer with the Roche Cobas c701 CLA for Na, K, Gluc and Lact and with the Sysmex XN-9000 CLA for ctHb. The grey dashed line denotes the line of equivalence and the red line the Passing-Bablok regression fit. The respective regression equations for each comparison and analyte are given in the black rimmed boxes.

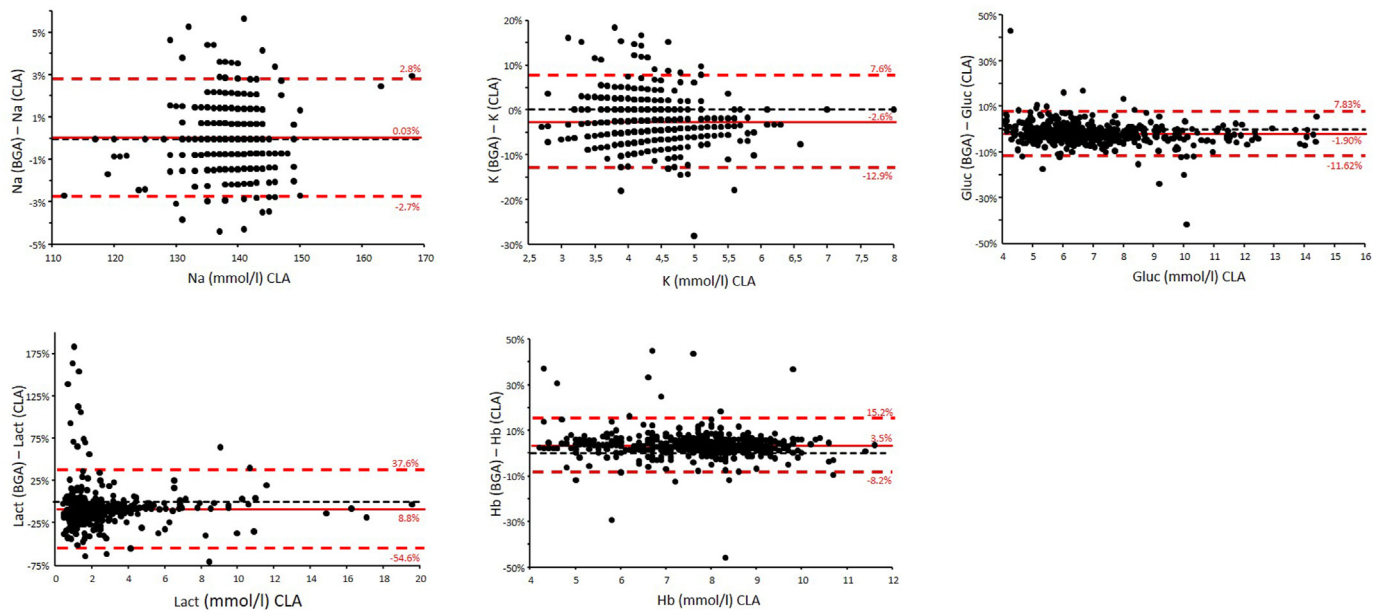


Figure 2. Bland-Altman plots for the method comparison the ABL FLEX 90 Plus Blood Gas Analyzer with the Roche Cobas c701 CLA for Na, K, Gluc and Lact and with the Sysmex XN-9000 CLA for ctHb. The black dashed line denotes the zero deviation between the BGA and CLA, while the red lines denote the mean relative deviation and its 95% limit of agreement (LoA).

Table 1. Summary data for the ABL FLEX 90 Plus BGA in comparison with the Roche Cobas c701 CLA for Na, K, Gluc and Lact and with the Sysmex XN-9000 CLA for ctHb. Given are the medians with inter-quartile ranges (IQR), the absolute (mmol/l) and relative (%) bias between BGA and CLA, their statistical significance level (P), as well as the corresponding 95% Limit of Agreement (95% LoA) and the interchangeability criteria ACL, TCL and RiliBÄK.

Analyte	median CLA (IQR)	median BGA (IQR)	bias	95% LoA	bias (%)	95% LoA (%)	P	ACL (%)	TCL (%)	RiliBÄK (%)
Na (mmol/l)	140 (138–142)	140 (138–142)	0.1	-3.8 to 3.9	0.03	-2.7 to 2.8	0.558	2.5	2.5	5.0
K (mmol/l)	4.1 (3.8–4.5)	4.2 (3.9–4.7)	-0.1	-0.6 to 0.3	-2.6	-12.9 to 7.6	<0.001	3.0	3.8	8.0
Gluc (mmol/l)	6.5 (5.6–7.9)	6.4 (5.5–7.7)	-0.1	-0.9 to 0.6	-1.9	-11.6 to 7.8	<0.001	3.3	4.0	15.0
Lact (mmol/l)	1.8 (1.2–2.5)	1.6 (1.1–2.3)	-0.2	-1.5 to 1.1	-8.8	-54.4 to 36.7	<0.001	5.5	14.7	18.0
ctHb (mmol/l)	7.9 (6.8–8.6)	8.1 (7.0–8.9)	0.3	-0.6 to 1.1	3.5	-8.2 to 15.2	<0.001	1.9	2.4	6.0

Table 2. Shown are the results of the indirect RI estimation for ABL FLEX 90 Plus BGA, the Roche Cobas c701 CLA (Na, K, Gluc and Lact) and the Sysmex XN-9000 CLA (ctHb). Given are the sample size (N), the lower and upper reference interval (LRI and URI), as well as their respective 95% confidence intervals (95% CI LIR and 95% CI URI). Also listed are the RI recommended by the manufacturers of the respective analytical test and analyzer platform (manufacturer RI).

Analyte	N	LRI	URI	95% CI LRI	95% CI URI	man-fact RI	
Na (mmol/l)	CLA	14425	137.0	145.0	135.1–139.0	143.0–147.0	136–145
	BGA	7844	135.3	146.1	133.0–137.6	143.7–148.5	136–145
K (mmol/l)	CLA	30090	3.43	4.87	3.30–3.60	4.70–5.05	3.4–4.5
	BGA	9795	3.22	4.84	3.08–3.36	4.65–5.03	3.4–4.5
Gluc (mmol/l)	CLA	37131	4.33	7.15	4.12–4.54	6.84–7.46	4.11–6.05
	BGA	26275	4.37	7.53	4.15–4.59	7.19–7.87	3.89–5.83
Lac (mmol/l)	CLA	6139	0.60	n.a.	0.53–0.66	n.a.	0.5–2.2
	BGA	26249	0.42	n.a.	0.37–0.47	n.a.	0.5–1.6
ctHb (mmol/l)	CLA men	32921	7.64	10.58	7.35–7.93	10.21–10.95	8.4–11.1
	BGA men	14259	7.57	11.21	7.25–7.89	10.78–11.64	8.4–10.9
	CLA women	36142	6.90	9.54	6.64–7.16	9.2–9.88	7.1–9.9
	BGA women	12269	6.37	10.26	6.07–6.67	9.83–10.69	7.4–9.9

size of 500 sample pairs. Even more important, these measurements were obtained under real-life clinical conditions, including all systemic and random pre-analytic factors, which might pass un-noticed in a classic method comparison study under controlled laboratory-only conditions.

The bias estimates for the BGA vs. CLA method comparison varied considerably for the different analytes, with Na having only a relative bias of 0.03%, which also did not differ significantly from zero. For all

other analytes the relative bias was much higher, ranging from 1.9% for Gluc, up to 8.8% for Lact and all differed significantly from zero. In addition, also the 95% LoA (the range within 95% of measurement differences are expected) for the measurements on the BGA and CLA showed marked differences between the analytes. The smallest 95% LoA was estimated for Na with +/- 2.8%, which, given that these results were obtained under field conditions on different analyzer platforms, is

impressively narrow. Second to Na were K, Gluc and ctHb which had similar 95% LoA estimates in the $\pm 10\%$ range around their mean differences. The highest 95% LoA by far with -54% – 38% was estimated for Lact, which also exhibited several extreme outliers in the low measurement range (below 2 mmol/l), as can be seen in [Figure 2](#). Applying the acceptance criteria to the estimated relative biases between BGA and CLA measurements, Na, K and Gluc are well below all 3 acceptance criteria, while Lact fails the ACL and ctHb both the ACL and TCL criteria. Even though RiliBÄK criteria seem too large to be clinically acceptable, we decided to not just use the most stringent criteria as the interchangeability criteria, because the RiliBÄK is a law-regulated guideline in Germany. However, in order to confine the relative broadly defined criteria of the RiliBÄK, we think that at least one of the two other criteria (ACL or TCL) should be met, thus ensuring that at least 95% of the clinical results fall within the total error budget.

Our results are thus divergent from the observations of previously published studies, where contradictory results were observed analyzing electrolytes values. Some studies showed that results differed significantly for sodium and chloride concentrations, or sodium and potassium concentrations, while others found significant differences just in potassium values [4, 13, 14, 15]. As such it is very important to know if two methods can be used interchangeably. In our case there was no clinical difference between measurements of sodium and potassium on ABL FLEX 90 Plus and core laboratory analyzer which is in concordance with several other studies [2, 4, 7, 8].

Maintaining normal or close to normal glucose levels is a priority in critically ill patients, reducing both morbidity and mortality [16, 17]. A variety of studies have compared the accuracy of different POC glucose measurements with other established laboratory methods [16, 17, 18, 19]. Caution should be taken especially for possible overestimations of blood glucose in low blood glucose measurements, masking hypoglycemia [3, 16, 17]. In our study, glucose measurements showed negligible variability in the results obtained, even though we did not test and compare glucose results based on the cut-off value for hypo-, normo- or hyperglycemia. Overall performance indicates that glucose measurement with ABL Flex 90 enables a rapid and accurate assessment of the patient's glucose concentration, with results close to those which would have been obtained with the Roche Cobas c701 central laboratory analyzers.

Rapid recognition of sepsis is of paramount importance, since it allows early treatment and reduces mortality [20]. Lactate concentrations increase with decreasing tissue perfusion due to anaerobic cellular respiration, making lactate an early warning indicator for directly assessing of shock severity and mortality rates [20]. While some studies have reported good correlation between POC whole-blood lactate and laboratory plasma lactate [3, 21], in our study the ABL Flex 90 Plus analyzers on average produced lower lactate values (bias 8.8%; LoA: -54.4% to 36.7%), albeit not on a clinically significant level, which is in accordance with the studies by Karon et al. and Leino et al. [4, 22]. The discrepancy in plasma lactate concentration in our study could be due to the fact that lactate is sensitive to a number of preanalytical variables which can result in falsely elevated values. The most critical factors influencing lactate results are stabilizing additives, temperature and storage time. Sampling protocols include sodium fluoride and potassium oxalate as preservatives, keeping the blood sample on ice until centrifugation, and separation within a maximum of 15 min [23].

Anemia is highly prevalent among emergency, surgery and critically ill patients, with developing subnormal hemoglobin levels by the third day of hospitalisation [24]. As a consequence, many of these patients receive red blood cell transfusions, with ctHb concentration being one of the most widely applied criteria for prescription. In our study, the ABL Flex 90 Plus analyzers yield higher values for hemoglobin than those reported by the Sysmex XN-9000 central laboratory analyzer. Other recent studies however, reported contradictory results, according to Zhang et al. there is no difference in ctHb concentration between POC and laboratory analyzers, while Leino et al. reported lower ctHb values for POC analyzers [4, 7], while our results are consistent with the study by Allardet-Servent et al.

in reporting higher ctHb values for POC analyzers [2]. Whole blood specimens used for blood gas analysis must be thoroughly mixed prior to analysis to achieve specimen homogeneity and to produce accurate measurement of hemoglobin. As such, specimens in which red blood cells have settled, can produce spurious results [25]. Since hemoglobin was systematically overestimated by the POC the use of laboratory analyzers should be preferred when deciding for red blood cell transfusions.

An essential part of the final postanalytical interpretation of a medical laboratory result analyte, is the reference range, universally used by laboratories for plasma or whole-blood measurements. In the absence of available RIs for BGA, a frequent practice is adopting general plasma/serum RIs. In the current study, we could show that indirect estimation of RIs for BGAs and CLAs resulted in similar and statistically indistinguishable RIs for Na, K, Gluc and ctHb (overlapping 95% CI of the LRI and URI, [Table 2](#)). For Lact the estimated indirect LRI for the BGA differed significantly from the LRI estimated for the CLA (non-overlapping 95% CI, [Table 2](#)), while the overall heavily skewed distribution of Lact values generally calls the usage of the RLE for this analyte into question.

In conclusion, our study showed for the tested analyzer systems, that the criteria for interchangeability were clearly met by Na, K and Gluc, which is congruent with the indirect reference intervals obtained with RLE for these analytes. For Lact and ctHb the picture however is not so clear-cut. While Lact passes the test of two of the used interchangeability criteria, its indirect RI is not interchangeable and the LoA between the two systems is very wide. ctHb fails two of the interchangeability criteria, even though its indirect RIs do not differ significantly between POCT and CLA and the LoA is relatively narrow. As such, the simultaneous use of results from ABL FLEX 90 Plus BGA and the CLA platforms Roche Cobas c701 and Sysmex XN-9000 seems advisable for Na, K and Gluc, while being questionable and not advisable for ctHb and Lact.

Declarations

Author contribution statement

Kocijancic Marija, Kraus Frank Bernhard: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Ludwig-Kraus Beatrice: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Data availability statement

The authors do not have permission to share data.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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