Letter to the Editor

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Management of potassium results in haemolysed plasma samples at the emergency department laboratory

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To the Editor,

Potassium (K) disorders, such as severe hypo- and hyperkalaemias, are medical emergencies with an increased risk of mortality that require an immediate electrocardiogram (ECG) and urgent treatment. K is one of the analytes most frequently measured at emergency department laboratories (EDLs), and sample haemolysis is a common issue complicating the analysis and interpretation of K results. The prevalence of haemolysed samples can reach 20% of all analysed specimens in an EDL and account for up to 70% of all unsuitable specimens [1, 2].

Some authors have proposed that in the setting of haemolysis, glomerular filtration rates (GFRs) >60 mL/min/1.73 m^2 in combination with a normal ECG is a reliable predictor of pseudohyperkalaemia and may eliminate the need for repeat testing [2]. However, other authors have pointed out that this approach will prevent identifying patients with hyperkalaemia and a normal GFR, and hypokalaemic patients [3].

Modern analysers used in clinical laboratories provide the haemolysis index (HI), which allows estimating the degree of haemolysis in analysed specimens [4]. As haemolysed samples are an important cause of economic and clinical issues in an EDL, it is necessary to develop effective pathways aimed at properly managing K results. The European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) Working Group of Preanalytical Phase (WG-PRE) has suggested a pragmatic approach for managing haemolysed sample results by providing a set of recommendations [5]. The Spanish Societies of Laboratory Medicine have also made some recommendations that include the use of correction equations, to obtain adjusted K concentrations that can be used to report informative commentaries, and to detect "critical values" that must be immediately communicated to the physician [6].

The aims of this study were to obtain a correction equation to estimate the K concentration in haemolysed plasma samples, to develop a pathway to properly manage interfered results, and to evaluate the performance of this approach. To obtain the correction equation, we collected the results for K and the HI obtained in lithium-heparin plasma samples assayed on a Cobas 6000®, c501 module (Roche Diagnostics), from 01/01/2015 to 31/12/2018 in the EDL of Hospital Universitario Central de Asturias (HUCA). These samples were from patients with a HI ranging from 50 to 1000 conventional units (1 conventional unit ≈ 1 mg/dL of haemoglobin), and with a second sample, non-haemolysed (defined as HI < 50 [7]), collected within 2 h of initial collection, according to the laboratory information management system. Results from samples analysed between January 2015 and December 2017 were used as a development cohort (n = 1093), meanwhile the results from 2018 were used as a validation cohort (n = 425).

Samples with a HI higher than 1000 conventional units were not used (recommendation 5.1 of EFLM WG-PRE) [5].

The equation obtained for the linear regression (Medcalc® v18.11.3) was $\Delta K\ (mmol/L) = 0.0279 + 0.0051 \times \Delta HI$ (conventional units), $r = 0.90$, $p < 0.001$ (Figure 1). The 95% confidence intervals (95% CI) for the intercept and slope were: [−0.0302 to 0.0860] and [0.0050–0.0053], respectively.

As the 95% CI for intercept included the origin, we simplified the formula to $\Delta K = 0.0051 \times \Delta HI$ and, therefore, the equation to obtain corrected K values

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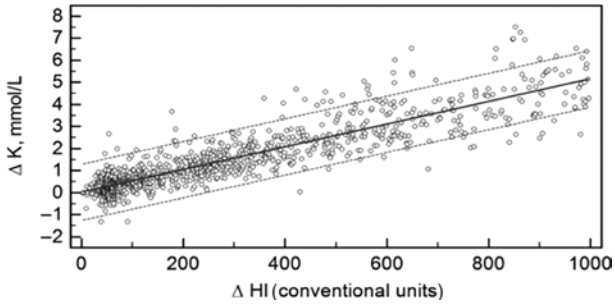

Figure 1: The figure shows the increase of plasmatic K concentration with the increment of haemolysis (haemoglobin level).
Linear regression line between the variation of potassium concentration (ΔK; ΔK = K [2nd sample] – K [1st sample]) and the variation of haemolysis index (ΔHI; ΔHI = HI [2nd sample] – HI [1st sample]), in two lithium-heparin plasma samples from the same patients (n = 1093), collected within 2 h with respect to the other.

was: $K_{corrected} = K_{measured} - (0.0051 \times HI)$. This equation was used to obtain corrected K values for samples assayed in 2018 (validation cohort) and these corrected K results were compared with the K concentrations measured in the second, non-haemolysed, sample.

When both results (measured and corrected K values) were compared ($[K_{corrected} - K_{measured}]/[K_{measured}]*100$), the differences observed (in percentages) were: first quartile (Q1 = – 6.6%), median (Q2 = – 0.3%), and third quartile (Q3 = + 8.5%), with some extreme differences (minimum = – 90% and maximum = + 209%). These corrected K concentrations (n = 425) were used to classify K results into five groups based on published reference interval in plasma (from 3.4 to 4.8 mmol/L) [8] and harmonised critical results limits (<2.8 and >6.0 mmol/L, for hypo- and hyperkalaemia, respectively) [9, 10].

These groups were defined as K < 2.8 ("very low"); K = 2.80–3.34 ("low"); K = 3.35–4.84 ("normal"); K = 4.85–6.00 ("high"); and K > 6.0 ("very high"). The proposed informative commentary to be reported instead of the K value is, "It is not possible to report the result of potassium due to the sample's haemolysis, but the concentration is probably ("very low"/"low"/"normal"/"high"/"very high"). We recommend sending a new sample to repeat the analysis".

The appropriateness of this interpretation was evaluated classifying the commentaries as:

- *Correct*: when the K value obtained in the second sample belonged to the assigned group.
- *Incorrect*: when the K value obtained in the second sample belonged to one group above or below the assigned group (i.e. low K interpreted as normal or very low); and
- *Very incorrect*: when the K value obtained in the second sample belonged to two groups above or below the assigned group (i.e. normal K interpreted as very low or very high).

The results obtained were: correct interpretation (n = 294, 69%), incorrect interpretation (n = 119, 28%) and very incorrect interpretation (n = 12, 3%). In addition, when the appropriateness of this interpretation was evaluated based on the HI of the initial sample (HI: <100, 101–249, 250–499, and 500–1000; groups created arbitrarily), it was observed that in samples with HI > 500, the percentage of misinterpretation was higher (40% "incorrect" and 7% "very incorrect" interpretations), probably due to higher variability of intracellular K release (Table 1). On the other hand, when interpretation was evaluated according to the actual K status (based on K concentration in the second sample), and focusing on patients with severe hypo- and hyperkalaemias, it was observed that in 20 cases of severe hyperkalaemia, 18 were classified as "very high" and two as "high" K concentration. Therefore, in all these cases the clinician would have received an interpretation of elevated K concentration, with 18 critical values. Similarly, there were six cases of severe hypokalaemia, with four being interpreted as "very low", one as "low", and one as "normal" K concentration. Therefore, five out of six cases were interpreted as reduced K concentration (four critical values) and one as normal. The clinical situation of this last patient, based on his medical records, seemed to have changed drastically between the first and second samples.

Table 1: Interpretation of commentaries for corrected K values based on results for HIs in the first samples and K values obtained in the second, non-haemolysed, samples.

		Interpretation		
Group	**n**	**Correct**	**Incorrect**	**Very incorrect**
HI: 51–100	83	60 (72%)	22 (27%)	1 (1%)
HI: 101–249	111	89 (80%)	20 (18%)	2 (2%)
HI: 250–499	131	92 (70%)	37 (28%)	2 (2%)
HI: 500–1000	100	53 (53%)	40 (40%)	7 (7%)
K: <2.80	6	4 (67%)	1 (16%)	1 (16%)
K: 2.80–3.34	17	7 (41%)	10 (59%)	0 (0%)
K: 3.35–4.84	310	224 (72%)	75 (24%)	11 (4%)
K: 4.85–6.00	72	41 (57%)	31 (43%)	0 (0%)
K: >6.00	20	18 (90%)	2 (10%)	0 (0%)
Total	425	294 (69%)	119 (28%)	12 (3%)

Haemolysis index (HI) in the first sample, potassium (K) concentration in the second sample.

When only results from samples with HI ≤ 500 conventional units (n = 325) were used, the calculation of diagnostic tests for detecting or excluding critical K values (K < 2.8 or >6.0 mmol/L) showed the following results: sensitivity = 0.87 (95% CI: 0.66–0.97), specificity = 0.96 (95% CI: 0.94–0.98), positive predictive value (PPV) = 0.65 (95% CI: 0.50–0.77), and negative predictive value (NPV) = 0.99 (95% CI: 0.97–1.00). Therefore, the main application of this approach is the exclusion of critical values.

In conclusion, the need to recollect a new, non-haemolysed, sample in the EDP increases costs, produces delays in discharges and postpones treatment and management decisions. However, not repeating the test may lead to fatal consequences for the patient when the blood K concentrations are abnormally elevated or reduced. Using informative commentaries based on corrected K results may help to identify those patients with increased risk of mortality (critical K values) whose tests need to be repeated as soon as possible. We do not recommend using the informative commentary when the HI is higher than 500 conventional units since the probability of misinterpretation is significant.

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