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RESEARCH ARTICLE

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The dilution evaluation as a corrective measure for interference in the white blood cell scattergram in Beckman Coulter DxH 900

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Abstract

Background: The Beckman Coulter DxH 900 is a haematological analyser capable of counting and sizing blood cells, and obtaining a complete blood cell count (CBC). This analyses different parameters of red blood cells (RBC), platelets and white blood cells/leukocytes. Some automated CBC counters present limitations due to specimen characteristics, abnormal cells or both factors. In the presence of abnormalities, the DxH 900 has a flagging system, warning the laboratory technician that something needs to be verified. In the present work, we evaluated samples from oncologic patients, presenting a population erroneously perceived as being lymphocytes. The most common explanations for this situation are RBC resistant to lysis or serum hyperbilirubinaemia.

Methods: In an attempt to solve and understand what the cause of this problem might be, we diluted our samples (1:3) and analysed the serum total bilirubin. To identify cells' abnormalities, the samples were also analysed by manual DLC counts. During the study, we also checked the different flags presented by the equipment.

Results: The results evidenced that the major interference was due to RBC lysis resistance, corresponding to 94.7% of the cases, while hyperbilirubinaemia was only present in 73.4%. Besides, we determined that some samples with normal bilirubin levels also presented interference, suggesting that hyperbilirubinaemia was not the main cause of the error. The most recurrent flag observed was "High event rate".

Conclusion: The dilution solved all of the observed interferences. The results between diluted and manual counts showed a strong correlation, leading us to introduce dilution in our laboratory routine.

KEYWORDS
dilution, high event rate, hyperbilirubinaemia, red blood cell lysis resistance, white blood cell scattergram

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1 | INTRODUCTION

Complete blood counts (CBC) are fundamental in haematology laboratories. Automated CBC assembles different technologies which allow the quick, accurate and cost-efficient method for CBC and differential leukocyte count (DLC).[1] The automated CBC counter used in our laboratory routine is the Beckman Coulter (BC) DxH 900. This automated haematology analyser conducts CBC and DLC analysis applying VCS (volume-conductivity-scatter).[2] CBC analysis is grounded on the Coulter principle, which uses the electrical resistance generated by particles to size and count cells and is used to assess red blood cells (RBC), white blood cells (WBC) and platelet count. VCS is obtained by the analysis of volume, conductivity and light scatter. The electric impedance method measures cell volume using low-frequency direct current. High-frequency electromagnetic current is used to measure conductivity, which is influenced by cells' internal structures. A monochromatic laser (helium-neon) serves as a light source for measuring the light scatter in five angles, which varies with cell shape, surface characteristics and cytoplasmic granularity. These tools are fundamental to generate the DLC, analyse reticulocytes and count nucleated red blood cells.[3,4]

Interferences in the haematology analysers lead to imprecise clinical results, and consequently, to inaccurate clinical decisions.[5] To avoid spurious results, the automated CBC presents a flagging system. Flagging is a sort of signalling system of the haematology analysers, warning the user that during the analytical process, outstanding events were detected and need verification.[6] The BC's haematology analyser is equipped with multiple algorithms to detect abnormal cells.[7] The literature describes that the automated CBC presents some limitations which could be related to specimen characteristics, abnormal cells or a combination of both.[8] The most acceptable and frequent explanations for these findings are associated with lipaemia, bilirubin or RBC resistance to lysis.[9,10] When RBCs are resistant to lysis, the WBCs are falsely higher and the scattergram presents dots located close to the lymphocyte region.[10] The RBC lysis resistance has been described in liver disease, abnormal haemoglobins, hyperlipaemia and newborn infants.[10–13] In liver disease, the cells commonly described as being associated with this resistance have been target cells (TC).[14]

Nonetheless, despite the improvements that have been developed over the years, the equipment is still unable to adequately discern the presence of lysis-resistant RBC.[11] To date, the most effective solution to solve these situations still is the dilution of the blood specimens, if possible, with the analyser's own diluent, in an appropriate factor.[8,11]

This study was conducted at the Portuguese Institute of Oncology of Coimbra Francisco Gentil, EPE, in which all the samples belonged to oncologic patients. Due to the characteristics of our population, spurious results may occur more frequently. In an attempt to try to overcome that interference, we subjected those samples to a corrective action, diluting them with the diluent of the equipment, as suggested in the literature.[8,11] We then analysed and compared the results of the WBC differential scattergrams on the samples pre-dilution and post-dilution and used the manual count obtained by blood smear observation as a reference method.

This study was developed with the objective of validating the corrective measure so that it could be implemented in our routine work. A second objective aimed to discover the cause of the interference, or at least exclude the most frequent associated interferences like bilirubin or lysis-resistant RBC.

2 | MATERIALS AND METHODS

2.1 | Sampling

This retrospective study (February 2021-May 2022) included a total of 208 samples of oncologic patients from the Portuguese Institute of Oncology of Coimbra Francisco Gentil, EPE. The samples, of venous blood, were obtained by a venous puncture, collected into Vacutainer tubes containing anticoagulant tri-potassium EDTA (K_3EDTA) and processed up to 2h after drawing. As the main focus of this study was validating the corrective measure developed in our laboratory, the samples were randomly selected. We only had taken into account the samples with a specific abnormal white cell scattergram. This study was approved by the hospital's Ethics Committee (TI 09/2023).

2.2 | Laboratory tests

All blood samples were processed using a BC DxH 900 cell counter. The BC DxH 900 is an automated haematology analyser that performs CBC analysis and VCS analysis. This equipment evaluates different parameters of RBC, platelets and WBC. It elaborates a scattergram that differentiates the various WBC into five subpopulations: neutrophils (NE), lymphocytes (LY), monocytes (MO), eosinophils (EO) and basophils (BA). The evaluation of the RBC and the WBC occurs in distinct areas, and the reagents used for the evaluation of these two blood cell types are also distinct. For evaluating WBC and performing the WBC differential, the BC DxH 900 uses the BC's DxH Diff Pack, a reagent that lysis erythrocytes and preserves the structure of leukocytes.[4] All samples were reprocessed after dilution (1:3) with BC's DxH Diluent.

As a reference method to identify cells' abnormalities, the samples were analysed by manual DLC counts. Blood smears were performed manually and stained using Aerospray Hematology® Slide Stainer/Cytocentrifuge (Model 7150) from Wescor® that uses Wright Giemsa staining. Differential count was made by microscope observation (Leitz Laborlux S) and 100 leukocytes were counted and categorized into segmented neutrophils, band neutrophils, lymphocytes, monocytes, eosinophils, basophils, metamyelocytes, myelocytes, promyelocytes and blast cells.

2.3 | Interference

To evaluate the possible interference caused by bilirubin, we analysed the samples' serum total bilirubin (TB) and direct bilirubin (DB). Both these measurements were obtained by a colorimetric method and were performed in Atellica® CH 930 Analyser, Siemens. Both tests are based on a chemical oxidation reaction that uses vanadate as an oxidizing agent. This oxidation reaction will result in a reduction in optical density that is proportional to the bilirubin concentration of the sample. The difference between them is the use of a surfactant agent in the total bilirubin reagent, which allows the solubilization and diazotization of indirect bilirubin, enabling its measurement.

In order to assess the hypothesis that poikilocytosis and possibly lysis-resistant RBC are the cause of the interference, we evaluated the morphology of the RBC in the blood smear.

To assess the liver status of patients, we also analysed the results from alkaline phosphatase (AP), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyl transferase (GGT) from the pre-diluted samples.

2.4 | Statistical analysis

We calculated the mean values of the different populations obtained on the various count methods applied in this study – PRD (pre-dilution), D (dilution) and MC (manual count).

Data analysis was performed utilizing Microsoft Office Excel 2010 and Stata version 18. The correlation between various methods across different populations was evaluated using Spearman's rank correlation coefficient. Comparative analysis of differences was conducted through the application of paired *t*-tests. Agreement between measurements was assessed via Bland-Altman plots (Figure S1). Furthermore, to elucidate the relationships among diverse variables, including interference and biochemical parameters, multiple linear regression analysis was employed.

Data selection for this research adhered to rigorous criteria, guaranteeing the inclusion of only comprehensive and dependable data sets. While acknowledging the significance and complexities of managing missing data in scientific inquiries, our approach in this instance strategically avoided the necessity for imputation by relying solely on analyses of unaltered and fully complete records.

3 | RESULTS

3.1 | WBC differential

A total of 208 samples with WBC scattergram interference were evaluated, where 51 (52.6%) were female and 46 (47.4%) were male. The mean age ± SD was 69.1 ± 10.1 years. Since our samples were randomly selected only according to their scattergram, some samples belonged to the same patient. These samples belong to oncologic patients, which included breast, colorectal, ovarian, pancreas and gastrointestinal cancers. This clinical information was consulted posteriorly to laboratory tests. We want to ensure that the main focus of this study was the corrective measure for the samples with interference and not the oncologic disease.

Mean values and standard deviation for PRD, D and MC were analysed for different cell populations (Table 1).

Between D and MC groups, we obtained a very strong correlation for NE ($r = 0.9$) and LY ($r = 0.91$), a strong correlation for MO ($r = 0.72$) and EO ($r = 0.70$) and a moderate correlation for BA ($r = 0.46$).

3.2 | Abnormal scattergram pattern

Scattergrams from samples with DLC interference presented lymphocyte populations dispersed and enlarged with fuzzy limits, involving debris area (Figure 1B). After dilution, the abnormal scattergram was modified, being comparable to one corresponding to a normal sample (Figure 1C). Observing this scattergram, we can notice that with the dilutions, all the DLC interferences were solved.

3.3 | Interference results

Out of the total number of samples analysed for interference, only 199 were measured for total bilirubin. From these 199 samples, 146 had a total bilirubin value above the normal range for our population, which is ≥1.2 mg/dL, corresponding to 73.4% of the cases. Target cells were the most frequent RBC poikilocytes observed, present in 197 samples, corresponding to 94.7% of the cases.

Table 2 presents the multiple linear regression coefficients for each biochemical variable (TB, DB, AP, AST, ALT and GGT) for NE, LY, MO, EO and BA. Each value represents the influence it has on each population of cells, and as we can see they present very low values, mainly without statistical significance.

3.4 | Analyser flags

The most frequent flag presented was the "High Event Rate" flag, which was present in 72.1% of DLC interference samples. Other identified prevalent flags were "Left Shift" and "Imm Grans", found in 32.7% and 24.5% of the cases respectively. Only 9.6% of the evaluated samples did not present any kind of flag.

4 | DISCUSSION

The general use of haematology analysers allows the haematology laboratories to obtain accurate and quick results.[8] Nonetheless, this type of equipment is still susceptible to unusual samples, leading to unreliable data and alarm flags.[8] In this study, we detected a scattergram population that was wrongly perceived as being lymphocytes.

TABLE 1 Mean ± SD, Median (IQR) for neutrophils, lymphocytes, monocytes, eosinophils and basophils for PRD, D and MC samples.

	PRD	D	MC	PRD – D			PRD – MC
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	*p*	Power	Mean ± SD
NE	59.78 ± 19.23	74.76 ± 14.5	75.5 ± 14.11	−14.98 ± 14.71	0.000**	1000	−15.72 ± 14.59
LY	28.7 ± 16.43	14.41 ± 10.48	15.2 ± 11.36	14.29 ± 13.26	0.000**	1000	13.5 ± 13.38
MO	8.84 ± 7.07	8.75 ± 4.73	7.23 ± 4.32	0.09 ± 6.12	0.825	0.056	1.61 ± 6.42
EO	1.24 ± 1.44	1.42 ± 1.84	1.23 ± 1.7	−0.18 + 0.75 ±	0.000**	0.941	0.01 ± 1.4
BA	1.14 ± 0.81	0.46 ± 0.44	0.53 ± 0.93	0.67 ± 0.83	0.000**	1000	0.6 ± 1.07

Note: Spearman Rho for PRD vs. D, PRD vs. MC and D vs. MC for all cell types. The statistical analysis used was paired t test and Spearman rho, *$p < 0.01$, **$p < 0.01$.

Abbreviations: BA, basophils; D, diluted samples; EO, eosinophils; IQR, interquartile range; LY, lymphocytes; MC, manual count; MO, monocytes; NE, neutrophils; PRD, pre-dilution samples; SD, standard deviation.

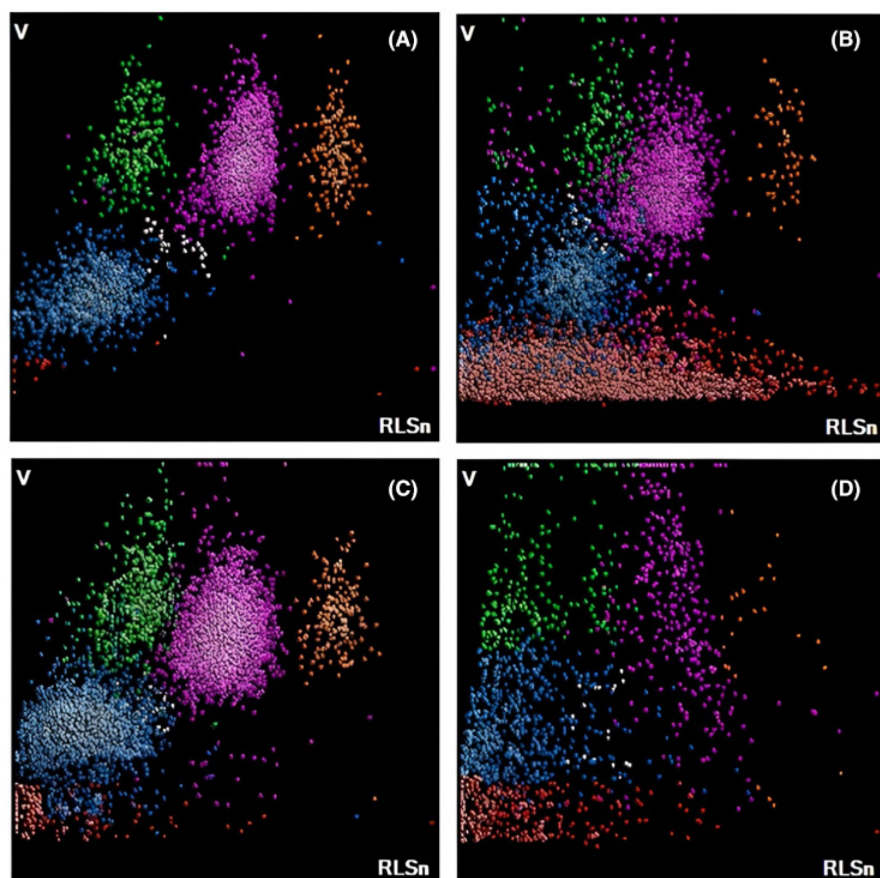

FIGURE 1 Examples of different WBC scattergrams obtained in the BC DxH 900. (A) WBC scattergram of a normal sample. The pink population correspond to neutrophils, the blue to lymphocytes, the green to monocytes, the orange to eosinophils and the white population, between the blue and the pink, to basophils. (B) WBC scattergram of a sample presenting interference. There is a population at the bottom left of the image that the analyser erroneously classified as lymphocytes (blue colour). (C) WBC scattergram of a sample presenting interference, after dilution. (D) WBC scattergram of a sample with bilirubin interference. There is dispersion of the signal pickup, and no cohesive and defined populations are present. RLSn, rotated light scatter; V, volume.

According to previous studies, the frequent causes related to these interferences are lipaemia, high bilirubin or RBC resistant to lysis.[9,10] Unusual WBC scattergrams were analysed in parallel with biochemical serum parameters and blood smear observation to point out the origin of this interference. In an attempt to exclude the most frequently associated interferences and aiming to obtain an adequate scattergram with reliable DLC, we diluted our blood specimens as a corrective action to interferences and reprocessed them in the BC DxH 900 haematology analyser.

The manual DLC count was used as a reference method, as was used in other studies.[3,7] This is the most frequently used method in laboratories, since another option could be to process the samples on another equipment, which involves costs and hospital's bureaucracies.

Our results (Table 1) are in agreement with preview studies since we found a high correlation between BC DxH 900 DLC and the manual counts for neutrophils, lymphocytes, monocytes and eosinophils (0.9, 0.91, 0.72 and 0.7 respectively); the same was true for

		D – MC			Spearman rho CI 95%		
p	Power	Mean ± SD	p	Power	PRD vs. D	PRD vs. MC	D vs. MC
0.000**	1000	−0.74 ± 5.63	0.029*	0.478	0.70** (0.62–0.76)	0.67** (0.59–0.74)	0.90** (0.87–0.92)
0.000**	1000	−0.79 ± 3.47	0.000**	0.905	0.60** (0.51–0.68)	0.58** (0.48–0.66)	0.91** (0.89–0.93)
0.000**	0.952	1.52 ± 3.06	0.000**	1000	0.72** (0.65–0.78)	0.56** (0.46–0.65)	0.72** (0.65–0.78)
0.476	0.050	0.19 ± 1.35	0.022*	0.528	0.87** (0.83–0.90)	0.60** (0.51–0.68)	0.70** (0.63–0.77)
0.000**	1000	−0.07 ± 0.74	0.100	0.250	0.28** (0.15–0.40)	0.19** (0.06–0.32)	0.46** (0.35–0.56)

TABLE 2 Mean ± SD, Median (IQR) for TB, DB, AP, AST, ALT and GGT.

Independent variables	Mean ± SD	Median (IQR)	Multiple linear regression coefficients				
			NE	LY	MO	EO	BA
Constant			7.69**	1.51*	0.34	0.32	0.01
D			0.90**	1.00**	0.78**	0.64**	1.37**
TB	9.89 ± 18.16	7.05 (1–13.9)	0.03	−0.43	0.40	0.14	0.03
DB	6.25 ± 5.93	5.45 (0.5–10.8)	−0.07	0.54	−0.46	−0.17	−0.05
AP	669.33 ± 636.65	502 (161–887)	0.00	0.00	0.00	0.01*	0.00
AST	141.86 ± 140.92	116 (38.5–175.5)	0.00	0.00	0.01*	0.00	0.00
ALT	87.03 ± 95.78	54 (23–108.5)	−0.01	0.01	0.00	0.00	0.00
GGT	665.54 ± 758.74	434 (78–976)	0.00	0.00	0.00	0.00	−0.01*
R^2			88.2%	90.7%	66.2%	54.5%	34.6%

Note: Multiple Linear regression: Dependent variable: MC; Independent variables: D, TB, DB, AP, AST, ALT, GGT (U/L) *$p < 0.05$; **$p < 0.01$. AP, AST, ALT, GGT (U/L), TB and DB (mg/dL).

Abbreviations: ABS, absolute value; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; BA, basophils; D, diluted samples; DB, direct bilirubin; EO, eosinophils; GGT, gamma glutamyl transferase; IQR, interquartile range; LY, lymphocytes; MC, manual count; MO, monocytes; NE, neutrophils; PRD, pre-dilution samples; R^2 squared R; SD, standard deviation; TB, total bilirubin.

basophils, for which in many cases it was not possible to build a regression to evaluate correlation.[14] Another study demonstrated that the correlation between automated CBC and the manual count was poor,[1] which is in accordance with our results. Since basophils are the cells in the smallest amount in WBC, these results were already expected.

Considering the WBC count, we did not evaluate the effect of the interference on it. However, previous studies concluded that this count was not altered by the interference in the differential count.[11] In fact, BC DxH 900 equipment has different cell lysing reagents for WBC counts and for WBC differentials.[4]

RBC lysis resistance is one of the principal factors responsible for the interference in the scattergrams,[11] together with bilirubin. However, our findings suggest that hyperbilirubinaemia is not likely the main cause of the observed interference or, at least, does not act alone. Despite the considerable number of samples that presented elevated bilirubin levels, the fact remains that several samples with normal values also showed interference in the scattergrams, and evidenced target cells in the blood smears. Also, a close look at the WBC scattergrams reveals a unique dot distribution that we associated with the actual bilirubin interference (Figure 1D), and is not similar in any way to the interference ones represented in Figure 1B.

Moreover, the scattergram pattern previously described for this interference is similar to the ones we observed in our study.[11] When considering our results, the presence of TC (94.7%) overcomes hyperbilirubinaemia (73.4%). The presence of TC in the majority of our samples and the effectiveness of the dilution as a corrective measure seem to be in agreement with this hypothesis. Additionally, our samples are from oncologic patients, whose liver function is impaired. In liver disease, the cells associated with RBC lysis resistance have been TC,[14] providing another justification for RBC lysis resistance as the main cause of DLC interference.

Results from Table 2 suggest a weak influence between biochemical variables on all WBC cell populations with liver parameters, leading us to conclude, once again, that bilirubin is not the main cause of interference.

The dilution is capable of overcoming the interference because it not only decreases RBC absolute number in the sample, which allows the lysing agent to act more efficiently, but also the levels of bilirubin. Nevertheless, to completely prove this hypothesis, we would need further studies to assess the resistance of the RBC, possibly with the use of different equipment and reagents. Another possible solution for this situation could be the extended lysis mode, available in other equipment (Abbott CellDyn 4000), which allows for a prolonged time of contact between the cells and the lysing agent.[2,12,15]

We also analysed the flags that appeared associated with our abnormal scattergrams. The flags with less frequency were "Left Shift" and "Imm Grans" in 32.7% and 24.5% of the cases respectively. In other studies, these flags were also present.[3,6] The "High Event Rate" was the most present one (72.1%). This occurs because an unknown quantity of RBC fragments is also taken into account for the DLC, increasing the number of events during the acquisition time. Previous similar studies also presented this kind of flag as the most frequent.[11] Taking this into account, we consider that a reflex test based on the flag "High Event Rate" could be developed, representing an improvement in routine work. This test would consist of an automated dilution of the samples presenting the "High Event Rate" flag, increasing efficiency and reducing response time, with the added bonus of avoiding extra labour for the laboratory technicians.

Due to our reality, our samples were all from oncologic patients, which we recognize could be a limitation. We also did not take into account the clinical history of the cases, and the impact that different pathologies or types of cancer could have on the results. For further studies, it would be interesting to cross the type of cancer with the results and try to establish a relation between the results and the oncologic disease.

5 | CONCLUSION

Our results suggest that the interference in the WBC scattergram relates more to RBC lysis resistance (presented as TC) than to the TB. The dilution solved the observed interference in all the cases, which may indicate that lysis reagent is not effective in destroying all the RBC. As statistical analysis evidenced a strong correlation between groups D and MC, we decided to introduce dilution as a corrective measure in our routine, and possibly establish a reflexive test in the near future. In a hospital, it is essential to have quick results and avoid false results to guarantee the best for the patient. So, our correction measure will allow the laboratory technicians and the pathologist to have accurate results without compromising waiting time.

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CONFLICT OF INTEREST STATEMENT

No conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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