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ORIGINAL ARTICLE

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"Bone marrow aspirate automated counts on hematology analyzers: formulating a scoring system based on hematology parameters, to discriminate reactive versus myelodysplastic syndrome-related bone marrows"

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Abstract

Introduction: Diagnosis of myelodysplastic syndromes (MDS) is usually challenging. In this context, we have attempted to employ data derived from automated analysis of bone marrow (BM) samples as an ancillary tool for the discrimination between reactive marrow and MDS.

Methods: A total of 101 BM anticoagulated samples referred for flow cytometry (FCM) analysis on the clinical suspicion of MDS had been previously counted in a Mindray BC-6800 hematology analyzer (testing set). Among them, 22/101 randomly selected BM samples (comparison set) had been also simultaneously counted by an Advia 2120 and a CELL-DYN Sapphire hematology analyzer. Selected parameters obtained by Mindray BC-6800 were retrospectively evaluated with ROC and regression analysis in an attempt to formulate a discriminative scoring system (SS) for MDS. This system was further evaluated in the comparison set.

Results: The diagnosis of MDS was established in 37/101 patients assessed ("MDS" group). Three patients were diagnosed with myelodysplastic/myeloproliferative neoplasm (MDS/MPN), while 61 revealed a "reactive" bone marrow ("RBM" group). Statistical analysis revealed significant differences in Hb, RDW-CV%, NRBC%, and RET% values between the "MDS" and the "RBM" group. Specific cutoff values were then indicated and employed for the formulation of a SS of high sensitivity (86.84%) and specificity (86.89%). The encouraging performance characteristics of the proposed SS were also confirmed in the BM comparison set.

Conclusion: Automated BM counts on hematology analyzers contributed to the formulation of a SS for the screening discrimination between reactive and MDS BM fluids, which seems to be applicable and informative, regardless of the analyzer used.

KEYWORDS

hematology analyzer, MDS, myelodysplastic syndromes, reactive bone marrow, scoring system

1 | INTRODUCTION

The proposed minimal diagnostic criteria proposed for the sufficient diagnosis of myelodysplastic syndromes (MDS) include two prerequisite criteria (both of which must be fulfilled), four major criteria (≥1 must be fulfilled), and three co-criteria (≥2 must be fulfilled, when major are not fulfilled), as described by Valent P. et al[1] Thus, the "MDS" diagnosis arises by the combination of clinical history, morphology assessment of peripheral blood and bone marrow (BM) smears, identification of typical multiparametric flow cytometry (FCM) patterns, typical histologic and immunohistochemical findings, as well as recurrent chromosome aberrations by conventional karyotype or fluorescence in situ hybridization (FISH), or/and typical somatic mutations.[1]

Among these criteria, the BM morphological assessment of dysplasia in at least 10% of all cells in one of the three hematopoietic lineages (erythroid, neutrophilic, and megakaryocytic) is hindered by subjectivity and interobserver variability, even among experienced hematologists. Besides, the correct application of all other methods is technically demanding and requires a highly trained staff. Hence, the potential utility of an automated hematology analyzer in the support of the MDS diagnosis would obviously be desirable.

In this study, automated counts of BM K2EDTA anticoagulated aspirates on the Mindray BC-6800 automated hematology analyzer (Mindray Bio-Medical Electronics Co., Ltd, Shenzhen, China) were evaluated for their usefulness to discriminate between reactive marrow and MDS. The formulation of a scoring system (SS) was further attempted based solely on the hematology analyzer's parameters. The resulting SS was finally evaluated for its applicability in the BM comparison set [automated counts obtained by an Advia 2120 (Siemens Healthcare Diagnostics, Deerfield, IL) and a CELL-DYN Sapphire (Abbott Diagnostics, Santa Clara, CA, USA) hematology analyzer].

2 | MATERIALS AND METHODS

2.1 | Patients and materials

During a twelve-month period, 101 patients (63 males/38 females, median age 67 years) had been investigated because of abnormal clinical manifestations and cytopenia(s) of obscure etiology. In all patients, initial clinical and laboratory assessment excluded a straightforward diagnosis, such as a deprivation or hemolytic anemia. In the context of the diagnostic work-up, a BM sample was obtained from each patient before any transfusion and sent for morphological evaluation, FCM, and cytogenetics. According to the final diagnosis, patients were allocated in the "MDS," the "myelodysplastic/myeloproliferative" ("MDS/MPN"), or the "reactive BM" ("RBM") group (Table S1). All BM K2EDTA anticoagulated samples referred for FCM analysis had been counted in a BC-6800 Mindray hematology analyzer (BM testing set), while 22 (of 101) randomly selected BM had been also counted in two additional hematology analyzers, an Advia 2120 (Siemens Healthcare Diagnostics, Deerfield, IL) and a CELL-DYN Sapphire (Abbott Diagnostics, Santa Clara, CA, USA) (BM comparison set). It should be noted here that patients with clotted BM specimens or with FCM-estimated high blood contamination [nucleated red blood cells on total cells (NRBC%) <2] were not included in the retrospective cohort of the 101 patients studied. Moreover, any patient that had been already transfused at the time of the first diagnostic investigation was also initially excluded from the retrospective cohort of patients studied, in order to avoid false deviations in red cell parameters.

2.2 | Methods

Final diagnosis was always documented by the combined evaluation of morphology, FCM, and cytogenetics.

2.2.1 | Morphology

All cases had been initially approached independently by two hematologists, both experienced in MDS diagnosis, in accordance with WHO criteria. They examined 500 BM nucleated cells in well-prepared Wright-Giemsa–stained smears and histologic sections of BM from all patients. Dysplasia was judged to be present in a lineage if 10% or more of BM nucleated cells of the corresponding lineage were dysplastic. If the two hematologists differed in their initial diagnosis for any patient, the respective smears were reexamined by them jointly and a consistent diagnosis was obtained.

2.2.2 | FCM

Flow cytometry had been routinely performed in all BM samples, according to the previously published recommendations,[2,3] in order to support the final diagnosis. A modified Ogata score was used with a FCM panel encompassing CD34, CD33, CD45, CD14, CD10, CD16, CD71, and CD66.[4] FCM had been performed on a 5-color flow cytometer (FC-500; Beckman Coulter, Miami, FL) with at least 150 000 events counted for each sample. Analysis had been performed with the CXP software (Beckman Coulter, Miami, FL).

2.2.3 | Conventional karyotype and FISH

In all cases, a conventional cytogenetic analysis had been performed on metaphases obtained from an unstimulated culture of anticoagulated marrow samples. On the same samples, an interphase FISH (i-FISH) had been also performed, using commercial probes for the detection of +8, −7/del(7q31), −5/del(5q31), and −17/del(17p13).

2.2.4 | Hematology analyzers

A residual amount from the anticoagulated (K2EDTA) BM samples referred for diagnostic FCM analysis had been counted on the hematology analyzers, no later than 4 hours after collection, in order to determine, among other parameters, the leukocyte count. Thus, the BM-automated counts were mainly performed in the context of

a leukocyte count assessment needed for further FCM analysis. All BM samples had been initially filtered with CellTrics® disposable filters (100 μm, Sysmex-Partec, Germany) to ensure the absence of cell debris, aggregates, lipid particles, or clots (Figure S1) and had been subsequently manually fed to the analyzers set in the whole blood mode. Additionally, FCM analysis had been always used to estimate the NRBC% and samples with NRBC% <2 were retrospective excluded from the final cohort, in order to avoid misinterpretation due to blood contamination.

2.2.5 | Mindray BC-6800 hematology analyzer

All adequate BM samples had been routinely counted in a BC-6800 hematology analyzer, and the obtained parameters were retrospectively compared between the "MDS" and the "RBM" group of patients. The Mindray BC-6800 provides classification of white blood cells based on the size of cells, their granularity, and content of nucleic acid. NRBC are counted separately, and basophils are counted in selected channels. The fluorescent stain allows the differentiation of reticulocytes on various levels of maturation.

To the best of our knowledge, BC-6800 hematology analyzer has been extensively and successfully evaluated for complete blood counting (including reticulocyte and NRBC enumeration), on peripheral blood, ascitic, pleural, cerebrospinal, and synovial fluids, but not BM fluids,[5-10] as with other analyzers. Besides, as stated above, in our case, the counted BM fluids were filtered residual samples collected for FCM and could not be used for extensive evaluation studies, mainly because of their limited quantity, in relation to their significant diagnostic value, but also taken into consideration ethical issues. Nevertheless, a within-run precision estimation was attempted in 20 residual BM fluids of adequate amount, which revealed acceptable (<5%) coefficients of variation (CV%) only for hematocrit (Hct, CV% = 0.90), hemoglobin concentration (Hb, CV% = 2.99), mean red cell volume (MCV, CV% = 0.70), red cell distribution width as a coefficient of variation (RDW-CV%, CV% = 0.74), platelets (PLTs, CV% = 1.89), reticulocytes' percentage (RET%, CV% = 3.12), NRBC% (NRBC%, CV% = 3.49), and white blood cells (WBC, CV% = 2.73). It should also be noted that FCM-induced NRBC% was significantly correlated with analyzer's NRBC% (data not shown). Moreover, flags on WBC were the most frequent flags generated (Figure S2), while WBC differential was not achieved in all samples and this was one of the main reasons why neutrophils were not evaluated for inclusion in the proposed scoring formula.

2.2.6 | Advia 2120 and CELL-DYN Sapphire hematology analyzers

Randomly selected samples had been also prospectively analyzed in two additional hematology analyzers: an Advia 2120 hematology analyzer (Siemens Healthcare Diagnostics, Deerfield, IL) and a CELL-DYN Sapphire (Abbott Diagnostics, Santa Clara, CA, USA). The results of these samples were retrospectively evaluated with the proposed SS, in order to compare its utility in "MDS" vs "RBM" discrimination, regardless of the analyzer used. All analyzers were calibrated and checked with daily controls, as per manufacturer's recommended guidelines.

2.3 | Statistical analysis

Descriptive analysis, Kolmogorov-Smirnov normality test, Mann-Whitney *U* test, ROC analysis, and multinomial regression analysis were performed with SPSS Statistics 17.0 (SPSS, Chicago, IL, USA). Cross tabulations and chi-square tests were performed for the determination of sensitivity (SN), specificity (SP), positive likelihood ratio (PLR), negative likelihood ratio (NLR), positive predictive value (PPV), and negative predictive value (NPV) of the final SS. Regression coefficients for a "MDS" diagnosis were used for the scoring panel. A value of $P < 0.05$ was considered statistically significant, wherever applicable.

3 | RESULTS

3.1 | Final diagnosis

According to the 2016 revision to the World Health Organization classification of myeloid neoplasms,[11] the final diagnosis of our cohort of patients was as follows: 37 MDS cases ("MDS" group), 3 cases with MDS/MPN ("MDS/MPN" group), and 61 cases with reactive BM fluids ("RBM" group). In particular, among the 37 patients of **MDS** group, nine patients were diagnosed with MDS with single lineage dysplasia (MDS-SLD), three with MDS with multilineage dysplasia (MDS-MLD), two with MDS-SLD and ring sideroblasts (MDS-RS-SLD), 10 with MDS-EB-1, 12 with MDS-EB-2, and one with MDS-del(5q). The **MDS/MPN** subgroup included three MDS/MPN unclassifiable cases, while the **RBM** group included 61 "reactive" marrow fluids (BM fluids that were finally evaluated as negative for a hematopoietic neoplasm). Demographic data, clinical data, and the respective hematological parameters that were counted in RBM samples are listed in Table S1. Regarding the MDS group, the karyotype was normal in 28 cases, +8 was found in 7 cases, and −7, del(7)(q31) and del(5)(q13q33) were detected in one case each. In all cases, i-FISH confirmed the cytogenetic findings.

3.1.1 | BC-6800 Hematology analyzer

Among all the available hematology parameters counted in the testing set of BM samples, the parameters which were selected to be further evaluated were as follows: Hb, MCV, RDW-CV%, PLTs, RET%, and NRBC%. Hb, RDW-CV%, NRBC%, and RET% values were statistically different between "MDS" and "RBM" patients ($P < 0.05$), while MCV and PLTs revealed no significant differences ($P = 0.186$ and $P = 0.059$, respectively) (Figure 1).

3.1.2 | ROC analysis

ROC analysis was performed to evaluate the cutoff points of maximum sensitivity and specificity, for each of the significantly different

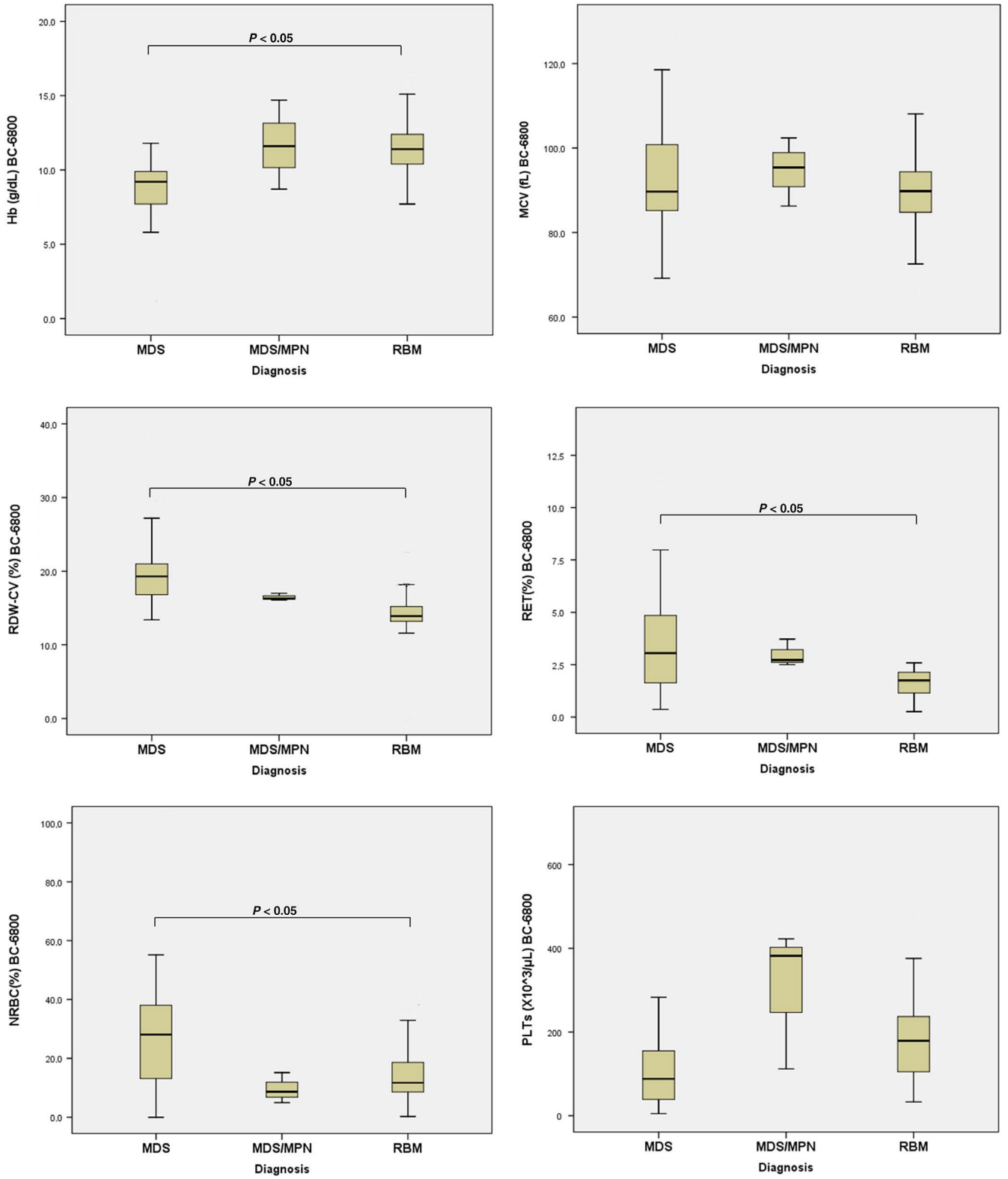

FIGURE 1 Hb, RDW-CV%, NRBC%, and RET% values revealed statistically significant differences between the "MDS" and the "RBM" group of patients ($P < 0.05$), while PLTs almost reached statistical significance ($P = 0.059$) [Colour figure can be viewed at wileyonlinelibrary.com]

hematology parameters, in order to better predict the "MDS" group. ROC analysis of Hb revealed an area under the curve (AUC) = 0.841, which corresponded to a Hb value of ≤10.4 g/dL, RDW-CV% had an AUC = 0.861, which corresponded to a value of ≥15.3%, NRBC% had an AUC = 0.731, which corresponded to a value of ≥13.3%, and RET% had an AUC = 0.694, which corresponded to a value of ≥2% (Figure 2).

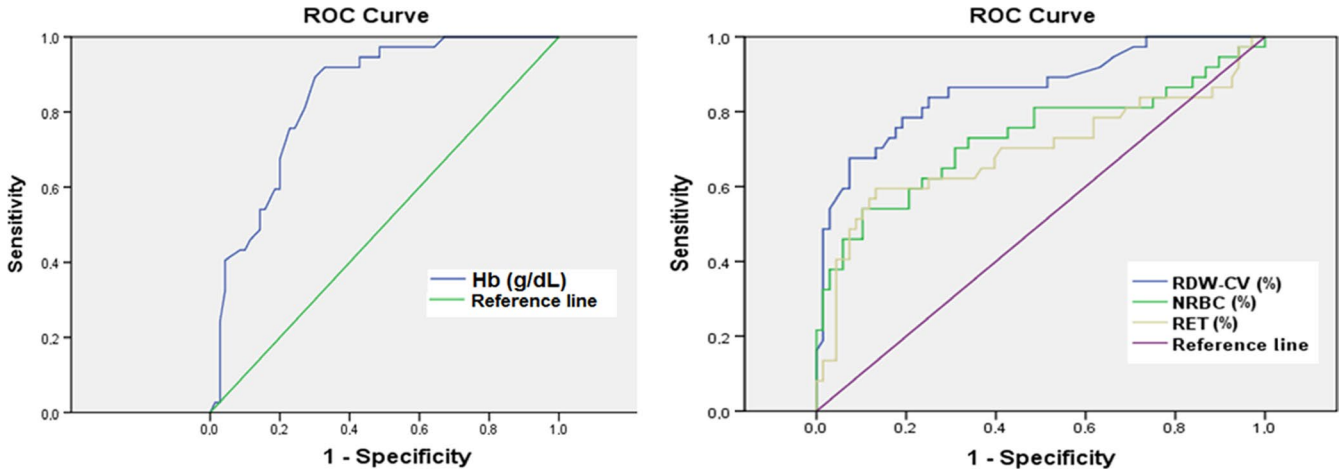

FIGURE 2 ROC analysis of Hb revealed an area under the curve (AUC) = 0.841, which corresponded to a Hb value of ≤10.4 g/dL, RDW-CV% had an AUC = 0.861, which corresponded to a value of ≥15.3%, NRBC% had an AUC = 0.731, which corresponded to a value of ≥13.3%, and RET% had an AUC = 0.694, which corresponded to a value of ≥2% [Colour figure can be viewed at wileyonlinelibrary.com]

3.1.3 | Multinomial regression analysis

Regression coefficients evaluated for the "MDS" diagnosis, compared to the RBM subgroup, were 0.563 for Hb (P = 0.004), 1.615 for RDW-CV% (P < 0.001), 1.59 for RET% (P = 0.07), and 1.018 for NRBC% (p = nonsignificant). Based on these coefficients, a point system was developed, as described below.

An optimal SS for the prediction of "MDS" was developed based on the following rules: Hb ≤ 10.4 g/dL (2 points), RDW-CV ≥ 15.3% (1 point), RET ≥ 2% (1 point), NRBC ≥ 13.3% (0.5 points), and PLTs ≤ 130 000/μL (0.5 points) (Table 1). PLTs were integrated in the formula, based on the mean value (±SE) of PLTs in the MDS group. A final score ≥3 revealed the best combination of SN (86.84%), SP (86.89%), PPV (80.49%), and NPV (91.38%), for a "MDS" diagnosis (Table 1). In particular, a final score ≥3 in our cohort of patients revealed 33 true-positive, four false-negative, eight false-positive, and 53 true-negative cases. It should also be noted that 2/3 (66.7%) patients of the "MDS/MPN" group had a score ≥3.

3.1.4 | Comparison set

The retrospective comparison of the SS was based on the retrospective analysis of the prospective and simultaneous BM counts, which had been obtained from two additional hematology analyzers. In particular, there were 22 randomly selected patients (out of 101), the BM of which had been simultaneously counted in an Advia 2120 and a CELL-DYN Sapphire hematology analyzer. The retrospective application of the SS, with the cutoff limit of ≥3, revealed the following results: for Advia 2120, three false negative out of 8 "MDS" and none false positive out of 12 "RBM" (62.5% SN, 100% SP) and for CELL-DYN Sapphire, two false negative out of 8 "MDS" and one false positive out of 12 "RBM" (75% SN, 91.7% SP) (Table 1). The remaining 2 "MDS/MPN" patients revealed ambiguous results, as only CELL-DYN Sapphire revealed a score ≥3 in 2 out of two patients (Table 1).

4 | DISCUSSION

Recently, fifth generation automated hematology analyzers appeared to provide additional easily accessible diagnostic information on dysplastic hematopoiesis.[12-15] Although the hematology parameters obtained by these automated hematology analyzers have been previously used for the identification of MDS, most of them concerned complete blood count (CBC) analysis and neutrophil distribution patterns.[12-15] The analysis of BM aspirates using automated blood cell counters has revealed variable pros and cons, but appears to be a promising ancillary diagnostic approach with significant potential advantages.[16] Due to the fact that a BM aspirate will probably not be avoided for a definitive MDS diagnosis, it is the first time in this study that BM aspirates have been counted in common hematology analyzers and counts have been correlated with a "MDS" or "non-MDS" diagnosis. Subsequently, an effort was made to formulate a screening scoring system, based solely on certain hematology analyzer's parameters, in order to discriminate reactive vs. MDS BM samples in routine clinical practice.

The parameters that were retrospectively selected for evaluation were Hb, PLTs MCV, NRBC%, RET%, and RDW-CV%. Due to the fact that persistent cytopenia in one or more hematopoietic lineages (red blood cells, neutrophils, and platelets) is considered as a prerequisite criterion for a "MDS" diagnosis,[1] it was suggested that at least two of these lineages should be represented in a screening formula. In this context, anemia (Hb) and thrombocytopenia (PLTs) were chosen to be evaluated. Parameters like absolute neutrophil count (ANC), monocytes (Mono), immature reticulocyte fraction (IRF), and immature platelet fraction (IPF) were not selected, because of the significant interanalyzer and intra-analyzer variability in ANC and Mono determination of most single dysplastic samples and because of the different technology of each analyzer for IRF and IPF determination, which would make the wide implementation of a SS impracticable. Additionally, the performance characteristics of WBC differential were not acceptable in BM fluid analysis; thus, neutrophils could not

TABLE 1 The proposed scoring system was consisted of five rated parameters, and the cutoff ≥3 was proposed to have the best sensitivity/specificity combination for an MDS diagnosis in the BM testing set (A). The distribution of patients with a final score ≥3, according to the analyzer used to obtain the parameters, is illustrated in (B). The comparative diagnostic performance of the recommended SS in relation to the analyzer used is shown in (C)

A

Parameter	Value	Score
Hb	≤10.4 g/dL	(+2)
RDW-CV%	≥15.3%	(+1)
NRBC%	≥13.3%	(+0.5)
RET%	≥2%	(+1)
PLT	<130 000/μL	(+0.5)
Sum		***≥3***

B

Score ≥ 3

BM testing set (N = 101)		**BM comparison set (N = 22)**		
	Mindray BC-6800		**Advia 2120**	**CELL-DYN Sapphire**
MDS (N = 37)	**33**	**MDS (N = 8)**	**5**	**6**
MDS-EB-1	*9*	*MDS-EB-1 (n = 1)*	*1*	*1*
MDS-EB-2	*12*	*MDS-EB-2 (n = 2)*	*2*	*2*
MDS-SLD	*6*	*MDS-SLD (n = 5)*	*2*	*3*
MDS-MLD	*3*	*MDS-MLD*	*NA*	*NA*
MDS-RS-SLD	*2*	*MDS-RS-SLD*	*NA*	*NA*
MDS-del(5q)	*1*	*MDS-del(5q)*	*NA*	*NA*
RBM (N = 61)	**8**	**RBM (N = 12)**	**0**	**1**
MDS/MPN (N = 3)	**2**	**MDS/MPN (N = 2)**	**0**	**2**

C

Diagnostic performance of the SS[a]

	Mindray BC-6800	Advia 2120	CELL-DYN Sapphire
SN	86.84%	62.50%	75.00%
SP	86.89%	100.00%	91.67%
PPV	80.49%	100.00%	85.71%
NPV	91.38%	80.00%	84.62%

Bold and italics indicate group and subgroup, respectively.
[a]comparisons were made between MDS and RBM groups.

be included in such a formula. Hb assessment revealed a strong correlation with MDS and had the highest relative burden in the final SS. Regarding PLTs, although the difference among the "MDS" and the "RBM" group did not reach statistical significance, PLTs revealed a lower median value in patients with MDS and were selected as a potential prerequisite parameter for an MDS diagnosis. It is reminded that in a previously published study of 2900 patients of the Duesseldorf MDS Registry, 43% of the patients had a platelet count lower than 100 000/microL.[17] Also, thrombocytopenia, attributable to ineffective platelet production by dysfunctional megakaryocytes, had been estimated to occur in 40%-65% of patients with MDS.[17]

MCV values did not prove to significantly differ among MDS and reactive BM and were avoided in the final SS, while NRBC% seemed to be significantly different among the "MDS" and the "RBM" group of patients. The value of NRBC% examination in BM has been also suggested by a previous study, where a differential proliferation index of NRBC was proposed for early/low-risk patients with MDS, showing increased proliferation, and advanced/high-risk patients with MDS.[18] Besides that, BC-6800 hematology analyzer has been previously recognized for its accurate and reproducible NRBC counts in high-value samples, such as patient monitoring samples used to determine the necessity of transfusion therapy in thalassemia patients.[19] Thus, although NRBC% was integrated in the final SS, it was associated with a lower point-system value due to its nonsignificant correlation coefficient.

The final additional parameters being evaluated for inclusion in a discriminative formula were RET% and RDW-CV%. The ineffective erythropoietic activity of BM in the "MDS" BM was expected to have a significant impact on the values of these two parameters. The counting of BM reticulocytes by hematology analyzers has been previously attempted twice.[20,21] Both studies indicated relatively higher reticulocyte counts in BM than in peripheral blood, especially in patients with MDS

or megaloblastic anemia.[20] In our data, RET% was statistically different among the "MDS" and the "RBM" group, while the calculated cutoff value for a "MDS" diagnosis was set at a relatively low level. Nevertheless, regression analysis revealed an almost significant correlation coefficient for RET%; thus, it was decided to be included in the final SS with a significant point-system value. Regarding RDW-CV%, it has been suggested that increased RDW in MDS might reflect dyserythropoiesis, associated with deregulated hemoglobin synthesis and iron metabolism.[22] Besides that, RDW (in peripheral blood) has been also proposed as an independent predictor of an MDS diagnosis.[23] The significant value of RDW-CV% as a discriminant hematological parameter was confirmed in our data. Thus, it was included in the respective proposed formula.

The retrospective application of the proposed SS in the testing set of BM samples revealed high SN, SP, PPV, and NPV for an MDS diagnosis. The investigation of false-positive and false-negative BM samples revealed that Hb was the only systematically identified factor that influenced the final score and classification. Also, it is important to notice that eight out of 11 patients with MDS-SLD had a score >3 and the same was true for nine out of 10 patients with MDS-EB-1. This was significant because these MDS categories were stronger candidates for subdiagnosis. The retrospective application of the same SS in the comparison set of BM samples, with the same cutoff value for a positive diagnosis, revealed even higher SP for an MDS diagnosis. However, a variance was observed in SN values among all analyzers, although acceptable. Additionally, the ambiguous results of the application of the proposed SS in the "MDS/MPN" group indicate the need for further investigation in larger patient cohorts. Overall, the difference in SN and SP of the SS among different analyzers may arise because of the need for different cutoff orientations. The analysis of larger patient cohorts in a broader range of analyzers will probably permit the identification of possible differences among the "non-MDS" BM reference ranges in parameters such as RDW-CV%, NRBC%, or RET%. This would probably result in different cutoffs, with subsequent differences in the calculated sensitivity and specificity of the proposed SS.

The establishment of a certain MDS diagnosis based on morphologic evaluation and FCM immunophenotyping remains challenging.[24] MDS should be diagnosed based on a combination of clinical history, morphologic features of myeloid cells, and additional laboratory data, always ruling out other diseases.[1,25] The straightforward diagnosis can be established in cases with significant increase in blasts or MDS-related cytogenetic abnormalities. However, there are several conditions other than MDS, which can induce an MDS-like BM morphological profile, and there are many cases lacking cytogenetic abnormalities.[26] Moreover, judging dysplasia requires professionally trained experts and could be affected by their subjectivity.[4,27,28] At the same time, FCM has been increasingly recognized as an ancillary diagnostic method in MDS diagnosis.[3,4,29] However, FCM is not always used in the routine diagnostic work-up in patients suspicious for MDS, while the panels proposed in analyzing MDS make MDS FCM complex, requiring a high level of expertise and high cost.[4]

In this context, automated BM counts on hematology analyzers appear to provide additional and easily accessible diagnostic information on dysplastic hematopoiesis. The application of a SS, based on five hematology parameters obtained by BM counts in classical hematology analyzers, appears promising in the initial screening diagnostic assessment of MDS, using erythrocyte and platelet counts, not ordinarily available from FCM. The proposed provisional SS could be evaluated in future studies, as an ancillary parameter or screening test in the assessment of marrow samples for MDS, along with other diagnostic modalities, and certainly not as a substitute for microscopic evaluation. Also, its evaluation in pre-MDS conditions, such as idiopathic cytopenia of undetermined (unknown) significance (ICUS), idiopathic dysplasia of unknown significance (IDUS), clonal cytopenia of unknown significance (CCUS), and clonal hematopoiesis of indeterminate potential (CHIP), would be of great interest.

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CONFLICTS OF INTEREST

The authors report no potential conflict of interest.

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SUPPORTING INFORMATION

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

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