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#### **ORIGINAL ARTICLE**

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# A new approach for diagnosing chronic myelomonocytic leukemia using structural parameters of Sysmex XN<sup>TM</sup> analyzers in routine laboratory practice

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#### ABSTRACT

According to WHO recommendations, diagnosis of chronic myelomonocytic leukemia (CMML) beforehand requires microscopic examination of peripheral blood to identify dysplasia and/or blasts when monocytes are greater or equal to  $1.0 \times 10^9$ /L and 10% of leucocytes. We analyzed parameters derived from Sysmex<sup>TM</sup> XN analyzers to improve the management of microscopic examination for monocytosis. We analyzed results of the complete blood count and the positioning and dispersion parameters of polymorphonuclear neutrophils and monocytes in 61 patients presenting with CMML and 635 control patients presenting with a reactive monocytosis. We used logistic regression and multivariate analysis to define a score for smear review. Three parameters were selected: neutrophil/monocyte ratio, structural neutrophil dispersion (Ne-WX) and monocyte absolute value. We established an equation in which the threshold of 0.160 guided microscopic examination in the search for CMML abnormalities with a sensitivity of 0.967 and a specificity of 0.978 in the learning cohort (696 samples) and 0.923 and 0.936 in the validation cohort (1809 samples) respectively. We created a score for microscopic smear examination of patients presenting with a monocytosis greater or equal to  $1.0 \times 10^9$ /L and 10% of leucocytes, improving efficiency in laboratory routine practice.

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#### **KEYWORDS**

Hematology; chronic myelomonocytic leukemia; disease diagnostics; microscopy; automated blood count

# Introduction

Chronic myelomonocytic leukemia (CMML) is a rare disease, with an estimated annual incidence of 0.4 cases per 100,000 individuals [1–3]. The biological diagnosis, defined in 2008 by the World Health Organization (WHO) and revised in 2016 is based on positive non-specific criteria: persistent monocytosis greater or equal to  $1.0 \times 10^9$ /L with monocytes accounting for  $\geq 10\%$  of the WBC count, dysplasia affecting at least one lineage in blood or bone marrow, blasts in bone marrow and/or in blood less than 20% and/or presence of a clonal abnormality. All other differential indications are negative criteria, namely: absence of reactive etiology to the monocytosis, absence of WHO criteria for myeloproliferative neoplasms and absence of PDGFR $\alpha/\beta$  or FGFR1 rearrangement [4–6]. Diagnosis of CMML requires a bone marrow examination, cytogenetic and molecular analysis, performed after blood smear examination. Bone marrow usually shows dysplastic abnormalities and excess of monocytes often with promonocytes and/or blasts. Cytogenetic abnormalities are present in 30–40% of cases [7] while molecular analysis shows abnormalities in more than 90% of CMML cases [8]. Identification of gene mutation markers permits risk stratification and may improve clinical decision making [9,10].

Reactive monocytosis represents the main differential diagnosis for CMML. It occurs in patients with bacterial, viral, fungal or protozoal infections, connective tissue disorders, hepatic diseases, extensive tissue necrosis, lipid storage

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#### Table 1. Baseline characteristics of the patients in the learning and validation cohorts.

	Learning cohort <sup>a</sup>			
	$CMML^{c}$ n = 61	Reactive monocytosis $n = 635$	p value <sup>d</sup>	Validation cohort <sup>b</sup> n = 1809
Age, median (range)	78 (39–91)	72 (29–99)		72 (18–106)
Gender, M/F	35/22 (NA = 4)	408/227		965/864
White blood cells count, median $n \times 10^9$ /L (range)	15.31 (3.33–200.40)	9.69 (-3.75-23.27)	.001	9.95 (2.10- 44.06)
Hemoglobin, median g/dL (range)	11.0 (7.5–15.1)	12.0 (5.7–18.9)	.008	12.2 (5.1–19.6)
Platelets count, median $n \times 10^{9}$ /L (range)	108 (19–431)	258 (5–1321)	<.0001	244 (2–1612)
CMML type 1/CMML type 2	45/12 (NA = 4)			24/2
Cytogenetic analysis, abnormal/normal/non-available	18/33/10			2/11/13
Molecular analysis, abnormal/non-available	4/57			2/24
Immunophenotype, Mo1 (Monocytes CD14 + CD16-) > 94%/<94%/NA	11/4/46			12/2/12
Dysplastic form/myeloproliferative form	26/35			14/12

<sup>a</sup>Patients with non-CMML hematologic malignancies were excluded.

<sup>b</sup>Including CMML patients (n = 26) and patients with other hematologic malignancies (n = 39).

<sup>c</sup>CMML patients were studied before any treatment.

<sup>d</sup>Mann-Whitney test.

disorders, hemolysis or bone marrow regeneration after chemotherapy [11,12]. These various circumstances create demands for many blood slide analyses, especially in the hospital environment where infectious and inflammatory diseases are common [13].

When the monocyte count is higher or equal to  $1.0 \times 10^9$ /L and  $\ge 10\%$  of the WBC count, examination of the blood smear is the first step to identify cytological arguments of CMML which can be discreet: dysplastic abnormalities, immature granulocytes, promonocytes and/or few blasts. Such analysis requires experienced laboratory staff and is subject to poor inter-operator reproducibility. In reactive monocytosis, a slide review is not necessary, provided that there is no flag on the analysis [13].

We hypothesized that a combination of parameters derived from Sysmex<sup>TM</sup> hematology analyzers may help to exclude the diagnosis of CMML and thus reduce the number of blood smears examined in cases of reactive monocytosis.

The objective of our study was to develop and test a scoring system based on the most relevant parameters able to distinguish CMML patients from patients presenting with a reactive monocytosis and to optimize microscopic examination of blood smears in cases of monocytosis.

#### Patients, materials and methods

#### **Patients**

Complete and differential blood count (CBC-DIFF) were analyzed in a learning cohort of 61 adults with a CMML diagnosis attending 11 centers in France and Belgium, and samples from 635 adult patients with reactive monocytosis analyzed at the Besançon laboratory between January 2014 and June 2016. The CMML diagnosis was established in all cases according to the 2016 WHO classification criteria [6]. All blood samples were taken before any treatment was given. All cases selected in reactive monocytosis group had monocyte count  $\geq 1.0 \times 10^9$ /L and  $\geq 10\%$  of the WBC count and came from emergency and intensive care departments, surgery or infectious wards. They had not been diagnosed with any hematological malignancy. Reactive monocytosis was confirmed since monocytosis was no longer apparent within 30 days after the first measurement. In order to validate the proposed scoring system, samples from a validation cohort of 1809 adult patients with a monocyte count  $\geq 1.0 \times 10^9$ /L and  $\geq 10\%$  of the WBC count analyzed at the Ambroise Paré university laboratory was used. Patients were prospectively included from February 2016 to November 2016, without any selection apart from the monocyte count criteria and age. Only the first CBC from each patient was included. Detailed characteristics of these three groups are shown in Table 1.

#### Materials

Peripheral blood samples were collected according to suppliers recommendations of preanalytic phase: blood was collected on distal venous puncture on ethylenediaminetetraacetic acid (EDTA), tubes were conveyed in transport boxes at ambient temperature and analyzed within six hours of collection, after storage at room temperature. The CBC-DIFF analyses were performed on Sysmex<sup>TM</sup> XN hematology analyzers (Sysmex Corporation, Kobe, Japan). XN analyzers provide a differential including polymorphonuclear neutrophils (Ne), polymorphonuclear eosinophils (Eo), polymorphonuclear basophils (Ba), lymphocytes (Ly), monocytes (Mo) and immature granulocytes (IG) by flow cytometry after capturing RNA-specific fluorochromes. Each cell is identified by its structural complexity (side scatter: SSC = X axis), its fluorescence intensity (side fluorescence: SFL = Y axis) and its size (forward scatter: FSC = Zaxis).

The Ne, Ly and Mo median positions on the three axes (Ne-SSC, Ne-SFL, Ne-FSC/Ly-X, Ly-Y, Ly-Z/Mo-X, Mo-Y and Mo-Z) as well as their dispersion (Ne-WX, Ne-WY, Ne-WZ/Ly-WX, Ly-WY, Ly-WZ/Mo-WX, Mo-WY and Mo-WZ) were measured by the analyzer (Figure 1).

The 11 centers were subject to an outsourced internal quality control: all analyzers were compared via an inter laboratory quality survey managed by Sysmex<sup>TM</sup> corporation which guaranteed the accuracy of all the studied parameters. All samples of the learning cohort were reviewed by microscopy. Smears were performed and stained using the



Figure 1. White blood cell differential (WDF) channel. On the left: Neutrophil scattergram showing scattergram median value (Ne-SSC) on the X axis and forward scattergram median value (Ne-FSC) on the Y axis. On the right: Neutrophil scattergram showing scattergram dispersion value (Ne-WX) on the X axis and fluorescence side scattergram median value (Ne-SFL) on the Y axis.

Sysmex<sup>TM</sup> SP10 blood smear maker. Two hundred cells were observed at 100× magnification by local experienced observers. Correlation between monocyte counts from the analyzer report and manual microscopic counts was then verified (data not shown). All parameters including analysis flags, positioning and dispersion parameters were evaluated. We focused on myeloid lineage differential count and structural parameters of neutrophils and monocytes.

#### Statistical analysis

Parameters were analyzed as quantitative variables and were summarized as median and range. The association between CMML status and the parameters was analyzed using logistic regression. A multivariable analysis was performed using a step-by-step ascending method. The internal validity of the model was achieved by discrimination and calibration using a Receiver Operating Characteristics (ROC) curve with Area Under the Curve (AUC) with its 95% confidence interval and the Hosmer-Lemeshow goodness-of-fit respectively. A score was calculated by applying the logistic function from the variables included in the multivariable model and the estimated coefficients. All the tests were two-sided at a 0.05 significance level. Analyses were carried out using R statistical software version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria, http://www.r-project.org)

# Results

#### **Bivariate analysis**

The median neutrophil count was not different in CMML patients and in controls (6.70 vs.  $6.39 \times 10^9$ /L, p = .5). The median monocyte count was significantly higher in CMML

patients than in controls (3.46 vs.  $1.16 \times 10^9$ /L, p < .0001). The neutrophil/monocyte ratio (Ne/Mo) showed a highly significant difference between the two groups (1.75 vs. 5.38 for CMML and controls respectively; p < .0001).

Differences in all positioning and dispersion parameters were statistically significant with p < .0001, except Mo-X (p = .000), Mo-WY (p = .011) and Mo-WZ (p = .001) (Table 2).

The median value of Ne-WX was higher in CMML than in reactive monocytosis (409 vs. 326). Out of all structural parameters, Ne-WX showed the highest discrimination power with an AUC of ROC of 0.973 (95% confidence interval (CI), 0.893–0.973; data not shown).

#### Multivariable analysis

Three variables previously selected for their discriminatory ability were confirmed: Mo absolute value, Ne/Mo ratio and structural Ne dispersion (Ne-WX) (Figure 2). Odds Ratios for these three variables were 3.89 (95% CI, 2.28–6.61) for Mo absolute value 0.25 (95% CI, 0.15–0.43) for Ne/Mo ratio and 1.32 (95% CI, 1.01–1.04) for Ne-WX, respectively.

## Defining a score

A statistical model using the three variables: monocyte count, neutrophil/monocyte ratio and Ne-WX, let us establish Equation (1):

$$\frac{1/(1 + \text{exponential} (-(-11.623 + 0.026 * \text{Ne-WX} - 1.385 * \text{Ne/Mo} + 2.714 * \text{Movalue})))}{(1)}$$

which allowed us to generate a score we called the 'monodysplasia score'. The discrimination of the model was excellent with an AUC of 0.988 (95% CI, 0.970-1.000).

	CMML Median (range)	Reactive monocytosis Median (range)	p value*
Neutrophil count (10 <sup>9</sup> /L)	6.70 (0.58–117.23)	6.39 (1.54–18.85)	.50
Monocyte count (10 <sup>9</sup> /L)	3.46 (1.02-39.8)	1.16 (1.00-2.76)	<.0001
Monocytes (%)	27.9 (10.1–62.6)	12.1 (10.0-28.5)	<.0001
Neutrophil/Monocyte ratio	1.75 (0.26–6.96)	5.38 (1.44-8.73)	<.0001
Immature granulocytes (%)	3.4 (0.0-20.5)	0.6 (0.0-13.9)	<.0001
Ne-SSC	140.9 (119.0–161.1)	150.0 (124.4–172.0)	<.0001
Ne-SFL	41.7 (33.0–55.9)	46.1 (32.3-84.1)	<.0001
Ne-FSC	78.1 (66.1–106.1)	86.1 (65.9–103.9)	<.0001
Ne-WX	409 (300–723)	326 (274–555)	<.0001
Ne-WY	807 (587–2236)	644 (553 – 553–1490)	<.0001
Ne-WZ	742 (597–1165)	655 (508– 923)	<.0001
Mo-X	120.9 (112.6–136.9)	118.3 (108.4–130.8)	.000
Mo-Y	119.9 (88.5–146.2)	110.8 (67.7–156.6)	<.0001
Mo-Z	65.5 (59.0–75.6)	63.8 (53.9–71.4)	<.0001
Mo-WX	247 (175–456)	262 (201–471)	<.0001
Mo-WY	682 (548–1289)	719 (516–2083)	.011
Mo-WZ	604 (433–765)	621 (418–1021)	.001

Table 2. Median, range and *p* values of quantitative, positioning and dispersion XN parameters in the learning cohort: CMML patients and patients with reactive monocytosis.

SSC: side scatter; SFL: side fluorescence scatter; FSC: forward scatter; Positioning parameters: Ne-SSC; Ne-SFL; Ne-FSC; Mo-X; Mo-Y; Mo-Z; Ly-X; Ly-Y; Ly-Z. Dispersion parameters: Ne-WX; Ne-WY; Ne-WZ; Mo-WX; Mo-WY; Mo-WZ. \*Mann-Whitney test.



Figure 2. Box-plots of the three most discriminant variables between CMML and reactive monocytosis. R:reactive monocytosis; Mo:monocyte blood count; Ne/Mo: neutrophil/monocyte ratio, Ne-WX:dispersion parameter of neutrophils on the X axis.

The Hosmer-Lemeshow goodness-of-fit test showed perfect calibration (p = .99). The ROC analysis provided a threshold of 0.160 beyond which a blood smear review should be triggered (Figure 3).

This value provided a sensitivity of 0.967 (95% CI, 0.880-0.997] with two false negative cases (3.3%) and a specificity of 0.978 (95% CI, 0.963-0.987) with 14 false positive cases (2.2%). The score was tested on the validation cohort of 1809 samples in which 26 cases of CMML were present and gave a sensitivity of 0.923 (95% CI, 0.745-0.988) with two false negative cases (7.7%) and a specificity of 0.936 (95% CI, 0.923-0.946] with 115 (6.4%) false positive cases.

# Discussion

The aim of this study was to define a new approach for monocytosis smear review in routine practice. Our findings indicate that, in addition to quantitative parameters such as monocyte count and the neutrophil/monocyte ratio, the XN structural parameter Ne-WX is helpful to distinguish CMML from reactive monocytosis. Ne-WX reflects polymorphonuclear neutrophil dispersion in terms of granularity on XN Sysmex<sup>TM</sup> analyzers. It is a highly sensitive parameter for identifying the coexistence of minimally granular neutrophils and normal neutrophils, in particular in cases where morphological abnormalities are difficult to identify by microscopic examination. Moreover, the analyzer flags are not efficient enough to detect these abnormalities since 12/61 CMML in the learning cohort and 8/26 CMML in the validation cohort showed a morphological analyzer flag.

Our findings allow us to make the following proposals: if the monocyte count is greater or equal to  $1.0 \times 10^9$ /L with monocytes greater or equal to 10% of the WBC count and our mono-dysplasia score greater than 0.160, then microscopic examination should be done to look for dysplastic abnormalities on all lineages. Conversely, if the monocyte count is greater or equal to  $1.0 \times 10^9$ /L with monocytes greater or equal to 10% of the WBC count and the monodysplasia score is 0.160 or less, then monocytosis is very likely to be of reactive origin and in the absence of any



Figure 3. Receiver operating characteristic (ROC) curve analysis of sensitivity and specificity of the mono dysplasia score established on the learning cohort (CMML and reactive monocytosis). The positive criterion refers to CMML status.

other flag, such samples do not need any microscopic examination.

Our scoring system, applied to the learning cohort, generated two false negative cases. One of them had a mild thrombocytopenia  $(140 \times 10^9/L)$  and the other one did not show any significant abnormality. The score generated 14 false positive cases representing 2.2% of the reactive group, which we consider to be an acceptable level of unnecessary blood smear reviews.

The validation cohort confirmed the results in terms of sensitivity and the two false negative cases had a platelet count lower than  $100 \times 10^9$ /L which would had been leading to a smear review. It showed less specificity with 6.4% of false positive cases. Of these 115 false positive cases, 34 (30%) were from patients with reactive monocytosis (sepsis) and 35 (30%) were from patients with hematological malignancies namely lymphoma (n=20), acute leukemia (n=9), myelodysplastic neoplasms (n=4) and myeloproliferative disorders (n=2).

In order to reduce unnecessary smear review in cases of monocytosis, the Groupe Francophone d'Hématologie Cellulaire (GFHC) recommends a blood smear review if monocytosis is greater than  $1.5 \times 10^9$ /L on the first hemogram or if it persists for more than 30 days [14]. In our learning cohort, 90 reactive monocytosis samples (14.1%) had a monocyte count greater than  $1.5 \times 10^9$ /L which would generate an unnecessary smear review, compared with only 14 (2.2%) using our proposed score. At the same time, 10 of the 61 CMML cases (16.4%) had a monocyte count of

 $1.5 \times 10^9$ /L or less. Only two of them had a 'blast/abnormal lymph' flag, leading to a smear review. Finally, combining our score and analyzer flags resulted in only two false negative cases (3.3%), while GFHC recommendations combined with the same analyzer flags lead to eight false negative cases (13.1%). Considering the validation cohort, performances of GFHC recommendations combined with analyzer flags were 0.731 (95% CI, 0.536–0.864) for sensitivity and 0.792 (95% CI, 0.772–0.810) for specificity. Use of these criteria would have generated 371 false positives (20.8%) and five false negatives (19.2%) while combining the score and analyzer flags revealed two false negative samples and only 6.4% false positive samples.

Previous studies have already assessed the use of WBC positioning parameters from other blood analyzers to screen for myelodysplastic syndromes [15,16]. Leroux et al described Ne-X (Ne-SSC) as a hypo-granulated neutrophil parameter on Sysmex<sup>TM</sup> XE 2100 analyzers [17]. In the present study conducted on XN analyzers, Ne-SSC did not demonstrate the same ability to identify neutrophil dysplasia in CMML, unlike Ne-WX. Another recent study has suggested that Ne-WX measurements from XN analyzers may be used in association with low hemoglobin concentrations to screen for MDS [18]. Shen et al. [19] used flow cytometry measurements to show that the structure of the granular lineage was reduced in patients with CMML]. Recently, Selimoglu-Bluet et al. [20] demonstrated the contribution of flow cytometry analyzing the repartition of monocyte subsets in peripheral blood and its interest in CMML diagnosis and follow-up . Further studies will be interesting to compare our scoring system with these recent flow cytometry analysis data.

CMML is an underdiagnosed disease with numerous complications. Diagnosis of CMML is necessary to prevent serious consequences such as infections and hemorrhagic complications and to delay the transformation into acute leukemia. Hypo-methylating drugs can reduce myelodysplastic-like features, while cytoreductive agents are used to control myeloproliferative forms [21].

Use of the 'mono-dysplasia-score' markedly improves the detection of CMML and decreases the number of useless blood smear reviews performed for monocytosis in adults. In cases with a positive score, the smear review is focused on confirming signs of dysplasia and searching for the presence of promonocytes and/or blasts, which greatly improves the efficiency of the laboratory.

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# **Disclosure statement**

No potential conflict of interest was reported by the authors.

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