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ORIGINAL ARTICLE

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Flow cytometry "Ogata score" for the diagnosis of myelodysplastic syndromes in a real-life setting. A Latin American experience

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Abstract

Introduction: Flow cytometry (FC) is a helpful tool for the diagnosis of myelodysplastic syndrome (MDS). Different FC score systems have been developed. The "Ogata score" is a simple diagnostic score that has been validated having a sensitivity of 69% and a specificity of 92% in low-risk MDS. We aimed to study the feasibility and the utility of the "Ogata score" for the diagnosis of MDS among Latin America (LA) Laboratories.

Grille Montauban and Lens contributed equally to this work.

*On behalf of the Grupo Latinoamericano de Síndromes Mielodisplásicos (GLAM).

Methods: This is a case and control study conducted in LA institutions members of Grupo Latinoamericano de Mielodisplasia (GLAM). A total of 146 MDS patients and 57 control patients were included. "Ogata score" was calculated.

Results: The sensitivity of "Ogata score" was 75.6% (95% CI, 66.8-81.3), specificity was 91.2% (95% CI, 79.7-96.7), PPV was 95.6% (95% CI, 88.5-98.3), and NPV was 65.4% (95% CI, 49.1-71.9). In low/intermediate-1 IPSS patients group, the sensitivity was 70.1% (95% CI, 60.2-78.2), specificity was 91.2% (CI-95%, 79.7-96.7), PPV was 94.2% (95% CI, 86.4-97.8), and NPV was 62.1% (95% CI, 53.0-78.7). In the group of patients "without MDS specific markers" (patients without ring sideroblasts, blast excess, or chromosomal abnormalities), the sensitivity was 66.7% (CI-95%, 55.8-76.0), specificity was 91.2% (95% CI, 79.7-96.7), PPV was 92.3% (95% CI, 82.2-97.1), and NPV was 63.5% (95% CI, 51.9-73.5).

Conclusions: The diagnostic power found in this study was similar to the reported by Della-Porta et al. Also in LA, the analysis was made in modern equipment with acquisition of at least 100 000 events which permits a good reproducibility of the results.

KEYWORDS
diagnosis, flow cytometry, Latin America, myelodysplastic syndrome, Ogata score

1 | INTRODUCTION

Myelodysplastic syndromes (MDS) are an heterogeneous group of clonal hematopoietic disorders characterized by dysplasia, bone marrow (BM) failure, and an increased risk of acute myeloid leukemia.[1] MDS diagnosis is challenging, especially in the absence of cytogenetic abnormalities, <5% of BM blast cells or <15% of BM ring sideroblasts. Many methods used to diagnose MDS patients, particularly cytogenetic and morphological assessment, depend on individual experience, and therefore, efforts should be made to identify novel diagnostic tools to make MDS diagnosis more accurate.

Multiparametric flow cytometry (FC) was introduced as an important diagnostic co-criteria, particularly in patients with morphology and/or cytogenetics inconclusive.[1] Current recommendations for MDS diagnosis support the use of FC as a valuable additional diagnostic tool.[2,3] Several FC scoring systems have been published to provide useful information for MDS diagnosis, having good sensitivity and specificity to discriminate MDS from other cytopenias.[4,5] Currently, many different FC scoring systems are available, containing a wide variability in terms of numbers and combination of markers used, the amount of parameters analyzed, and the weight assigned to each parameter.[3,5,6] European Leukemia Net Working Group for FC in MDS (IMDSFlow) recommend the Ogata scoring system for screening purposes.[7] This score includes four parameters: percentage of CD34+ myeloid progenitor cells among total nucleated cells; percentage of B-cell progenitors within the CD34+ subset; CD45 expression on myeloid progenitors compared to its expression on lymphocytes; and side scatter (SSC) of granulocytes compared to SSC on lymphocytes.[8] The Ogata score for low-grade MDS was validated in a large multicenter study which turned out with very good reproducibility and a sensitivity of 69% and a specificity of 92%.[9]

The aim of this study was to evaluate, in a real-life setting, the utility of the "Ogata score" for the diagnostic of MDS among Latin America (LA) Laboratories.

2 | MATERIALS AND METHODS

2.1 | Study design and patients

This is a cross-sectional, case and control study conducted in nine LA institutions members of Grupo Latinoamericano de Mielodisplasia (GLAM) from Argentine, Brazil, Colombia, Mexico, and Uruguay. A total of 146 patients (69 men and 77 women) with MDS or myelodysplastic/myeloproliferative neoplasms (MDS/MPN) diagnosis with a median age of 69 ± 27 years were included. The diagnosis of MDS or MDS/MPN was established based on clinical data, morphology, and cytogenetics following the 2008 and updated 2016 WHO criteria.[10,11] As shown in Table 1, patients were classified according to the 2016 WHO criteria,[10] International Prognostic Scoring System (IPSS), and revised IPSS.[12,13] As MDS diagnosis in patients without specific markers is more difficult to reach, we create a variable named "MDS without specific markers" which includes patients with refractory cytopenia with unilineage or multilineage dysplasia without ring sideroblasts, blast excess, or chromosomal abnormalities to evaluate the utility of the "Ogata score" in this group.

Also, 57 control patients (pathological controls without MDS) were included (Table 1). Controls were selected in accordance with

TABLE 1 Patients and controls characteristics

	Patients (n = 146)	Controls (n = 57)	*P* value
Age (median ± IQR)	69 ± 27	65 ± 23	NS
Male/female	69/77	25/32	NS
Control disease			
Anemia associated with chronic disease		10 (17.6%)	
Cytopenia associated with autoimmune disease		8 (14.0%)	
Anemia associated with renal insufficiency		6 (10.5%)	
Anemia associated with infectious disease		11 (19.3%)	
Aplastic anemia		2 (3.5%)	
Non-clonal cytopenia		20 (35.1%)	
MDS WHO 2016 classification			
MDS-SLD	11 (7.6%)		
MDS-MLD	84 (57.2%)		
MDS-RSMLD	3 (2.1%)		
MDS-EB	35 (24.1%)		
MDS with isolated del(5q)	4 (2.8%)		
CMML	7 (4.8%)		
MDS/MPN-RS-T	1 (0.7%)		
MDS/MPN unclassified	1 (0.7%)		
IPSS			
Low	39 (26.7%)		
Intermediate-1	78 (53.5%)		
Intermediate-2	24 (16.4%)		
High	5 (3.4%)		
R-IPSS			
Very low	23 (15.7%)		
Low	59 (40.4%)		
Intermediate	28 (19.2%)		
High	21 (14.4%)		
Very high	15 (10.3%)		

Note: Data shown are absolute frequency and percentage.
Abbreviation(s): CMML, chronic myelomonocytic leukemia; IQR, interquartile range; MDS/MPN-RS-T, MDS/MPN with ring sideroblasts and thrombocytosis; MDS-EB, MDS with excess blast; MDS-MLD, MDS with multilineage dysplasia; MDS-RSMLD, MDS with ring sideroblasts and multilineage dysplasia; MDS-SLD, MDS with single lineage dysplasia; NS, not significant.

the European Leukemia Net (ELN) recommendations.[2] The control group included patients with anemia associated with chronic disease, immune cytopenias, renal insufficiency, infectious disease, aplastic anemia, and other non-clonal cytopenias (Table 1).

The study was approved by the Medical Ethics Committee of each participants' institutions.

2.2 | "Ogata score"

As we want to demonstrate the real-life value of the score, methods for processing, handling samples, acquisition, and analysis were carried out by each center in accordance with their usual practice. BM cells were aspirated into a heparinized syringe or collected in ethylenediaminetetraacetic acid (EDTA) tubes. All laboratories processed samples within 24 hours after bone marrow aspiration and stored it at room temperature. For lysis of the non-nucleated red blood cells, ammonium chloride (either home-made or commercially available) was used. All laboratories but one used stain-lyse-wash procedure and this one used lyse-stain-wash procedure. At least 100 000 cell events were acquired, but 50% of the laboratories acquired more than 300 000 cell events. Data were analyzed using either INFINICYT software (Cytognos) or FLOWJO software (BD Biosciences). Cytometers used to acquire samples for this study were FACS Canto II (BD Biosciences), FACS Calibur (BD Biosciences), and Navios (Beckman Coulter).

The "Ogata score" was calculated following the analytical strategy previously described.[9] A score of one point was added for each of the following four parameters: (a) percentage of CD34+ myeloblasts in all nucleated cells ≥2%; (b) percentage of CD34+ B-cell progenitors in CD34+ gated cells ≤5%; (c) ratio: mean fluorescence intensity (MFI) of CD45 on lymphocytes/MFI of CD45 on gated CD34+ myeloblasts ≤4 or ≥7.5; and (d) ratio: SSC peak channel on total granulocytic cells (CD10+ and CD10−)/SSC peak channel of lymphocytes ≤6. Most of the laboratories added other markers to better identify myeloblasts (CD33 and/or CD117) and B-cell progenitors (CD19 and/or CD10). A score of ≥2 points was considered positive for MDS diagnosis.[9]

2.3 | Statistical analysis

Categorical variables were expressed as frequencies and percentages and quantitative variables as median and interquartile range (IQR). For categorical variables, the statistical significance of differences was evaluated using chi-square test and for continuous variables using Mann-Whitney test. A value of $P < 0.05$ was considered as statistically significant. To estimate the diagnostic power of the "Ogata score," the following parameters were calculated: specificity, sensitivity, positive predictive value (PPV), and negative predictive value (NPV). To define the clinical utility of the score, the positive likelihood ratio (LHR+) was calculated. One limitation of our study is the small number of controls included, not achieving a patient:control ratio 1:1. For the hypoplastic subgroup analysis, we randomly reduced the control group sample size in order to reach a patient:control ratio 1:2. Analyses were performed using SPSS 21.0 software.

3 | RESULTS

We first considered all 146 MDS patients, and we found that the sensitivity of "Ogata score" was 75.6% (95% CI, 66.8-81.3), specificity

TABLE 2 Diagnostic power of "Ogata score"

	n of patients/ controls	"Ogata" Score value (median ± IQR)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	LHR+ (95% CI)
All MDS patients	146/57	2 ± 1	75.6% (66.8-81.3)	91.2% (79.7-96.7)	95.6% (88.5-98.3)	65.4% (49.1-71.9)	8.3 (3.7-18.2)
MDS without specific markers of dysplasia	90/57	2 ± 1	66.7% (55.8-76.0)	91.2% (79.7-96.7)	92.3% (82.2-97.1)	63.5% (51.9-73.5)	7.6 (3.2-17.8)
IPSS low and intermediate-1	117/57	2 ± 1	70.1% (60.2-78.2)	91.2% (79.7-96.7)	94.2% (86.4-97.8)	62.1% (53.0-78.7)	7.9 (3.4-18.2)
IPSS intermediate-2 and high	29/57	3 ± 1	96.5% (80.4-99.8)	91.2% (79.7-96.7)	84.8% (67.3-94.3)	98.1% (88.6-99.9)	11.0 (4.7-25.5)
R-IPSS very low, low and intermediate	110/57	2 ± 1	69.9% (59.1-77.5)	91.2% (79.7-96.7)	93.7% (85.4-97.7)	60.3% (51.7-70.4)	7.8 (3.4-17.1)
R-IPSS high and very high	36/57	3 ± 1	94.4% (79.9-99.0)	91.2% (79.7-96.7)	87.2% (71.7-95.1)	96.3% (86.2-99.4)	10.8 (4.6-24.9)
Hypoplastic MDS	13/26	2 ± 1	72.7% (39.3-92.6)	85.1% (63.7-95.2)	61.5% (32.2-84.8)	89.4% (68.7.9-96.9)	5.9 (2.2-11.9)

Abbreviations: CI, confidence interval; IPSS, International Prognostic Scoring System; IQR, interquartile range; LHR+, positive likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; R-IPSS, Revised International Prognostic Scoring System.

was 91.2% (95% CI, 79.7-96.7), PPV was 95.6% (95% CI, 88.5-98.3) and NPV was 65.4% (95% CI, 49.1-71.9) and LHR+ 8.3 (95% CI, 3.7-18.2), (Table 2). We emphasize that 80.2% (117/146) of MDS patients included in this study were patients with IPSS low or intermediate-1 risk. Then, we analyzed 90 MDS patients without specific markers of dysplasia and the sensitivity of "Ogata score" dropped to 66.7% (CI-95%, 55.8-76.0), PPV to 92.3% (95% CI, 82.2-97.1), LHR+ to 7.6 (95% CI, 3.2-17.8) with similar specificity and NPV (Table 2).

Considering patients stratified according to IPSS, the sensitivity of the "Ogata score" in IPSS low/intermediate-1 (Int-1) risk group was lower than in the intermediate-2 (Int-2)/high-risk group, 70.1% (CI-95%, 60.2-78.2) and 96.5% (95% CI, 80.4-99.8), respectively. Similar results were found with the NPV 62.1% (95% CI, 53.0-78.7) and 98.1% (95% CI, 88.6-99.9) in low/Int-1 and Int-2/high-risk group, respectively, and with the LHR+ 7.9 (95% CI, 3.4-18.2) and 11.0 (95% CI, 4.7-25.5) in low/Int-1 and Int-2/high-risk group, respectively. Comparable results were found when patients were stratified by revised IPSS score (Table 2).

Although only 13 patients with diagnosis of hypoplastic MDS were included, we evaluate the diagnostic power of the score in these patients, founding that the sensitivity, PPV, and LHR+ were low (72.7% [95% CI, 39.3-92.6], 61.5% [95% CI, 32.2-84.8], and 5.9 [95% CI, 2.2-11.9], respectively).

4 | DISCUSSION

Bone marrow multiparametric FC gives complementary information for both MDS diagnosis and prognosis, and it has been introduced as an important co-criteria for MDS diagnosis.[1,6,8,14-18] To date, FC in MDS still requires a high level of expertise to analyze and interpret the results, making their daily use in the clinical work-up of MDS diagnosis difficult.[19,20] Scoring systems can simplify the interpretation of the results and provide useful information for the diagnosis of MDS, with good sensitivity and specificity to discriminate MDS from other cytopenias.[4,9,21-27]

In this study, we report the results of the diagnostic utility of the "Ogata score" in the real-life routine diagnosis in LA. In contrast to clinical trials, here, the handling samples, processing methods, acquisition, or cytometric analysis have not been harmonized. All these steps were carried out by each center in accordance with their usual practice.

Similar to the results reported by Della Porta et al,[9] in this real-life setting, we found a sensitivity of 70.1%, specificity 91.2%, PPV of 94.2%, NPV of 62.1%, and LHR+ of 7.9 in low/Int-1 IPSS patients, showing how robust this score is. It was noted that the score tended to be better in Int-2/high IPSS patients, with a sensitivity of 96.5% and a LHR+ of 11, suggesting that, as previously reported, BM dysplasia detected by FC increases with disease progression.[5,28] The higher "Ogata score" in high-risk patients was mainly due to an increase in myeloid progenitor cells and a decreased in B-cell progenitor compartments. Similar results were found using the revised IPSS score (Table 2).

Focusing our analysis on patients who are very difficult to diagnose in clinical practice like those without specific markers of dysplasia (such as patients without ring sideroblasts, excess of blasts, or chromosomal abnormalities), the diagnostic power of this score is lower than in whole population (sensitivity is 67%, specificity of 91%, and LHR+ 7.6), but is similar to data previously reported by Della Porta et al.[9]

Hypoplastic or hypocellular MDS is another interesting population, which represent around 10%-15% of total MDS patients. This entity is characterized by decreased marrow cellularity and is often difficult to distinguish from aplastic anemia based on standard morphological criteria.[29]

Although we examined the value of "Ogata score" in this subgroup and we found a low PPV and LHR+, a larger number of patients is needed to determine its real diagnostic power.

We believe that setting up the "Ogata score" is technically easy, time- and cost-efficient, making it suitable for general use in LA laboratories. Additionally, its reproducibility has already been demonstrated by different groups.[9,23,30,31]

One important drawback of the "Ogata score" is that the sensitivity is not very high, mainly in low-risk MDS patients. Hence, many research groups are working on its improvement. Bardet et al[30] have reported that the addition of two new variables (CD7 aberrant expression on myeloid progenitors and CD56 on monocytes) improve the score sensitivity. Recently, Ogata et al[32] have also reported that adding the CD33 expression on CD34+ cells as a fifth parameter (called granulocyte/CD34 cell CD33 ratio) to the classic four parameters improves it sensitivity. Another strategy in order to increase the MDS diagnosis sensitivity is to combine two FC scores (eg, Ogata and Red Score improve the sensitivity to 88%).[23] Another study evaluating the combination of the "Ogata score" with the erythroid parameters recommended by IMDSFlow working group (CD36 and CD71 distribution, CD36 expression on erythroid lineage and CD117+ erythroid precursors) showed an improved diagnostic power (sensitivity of 86% and specificity of 95%).[33] Furthermore, integrating the "Ogata score," "Wells FCSS," and the erythroid parameters recommended by IMDSFlow working group, into the so-called Integrated Flow Cytometry score (iFCs), showed 80% sensitivity and 95% specificity.[34] We are now planning to incorporate the Red Score[23] in order to improve the sensitivity of the "Ogata score" among LA laboratories.

In conclusion, similar diagnostic power with "Ogata score" as those already published in clinical trials was obtained in our patients.[9] Altogether, our results show that the "Ogata score" is simple, reproducible, and technically robust in routine diagnosis supporting its use for MDS diagnosis in conjunction with clinical information, blood and BM smear cytology, BM biopsy, cytogenetics and molecular genetics.

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CONFLICT OF INTEREST

The authors have no competing interests.

AUTHOR CONTRIBUTION

SG and DL conceived the presented idea. SG designed and made the database, collected clinical data, analyzed the data, and wrote the manuscript. CRHP, EV, JG, LS, JCS, RC, AE, MB, DI collected clinical data. VN, ILM, VC, AB, LJRC, NB, NT, RG, JRV, FGPC, VF, BV, AN analyzed flow cytometry files and calculated Ogata score. DL analyzed the data and wrote the manuscript. All author revised, corrected and approved the manuscript.

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