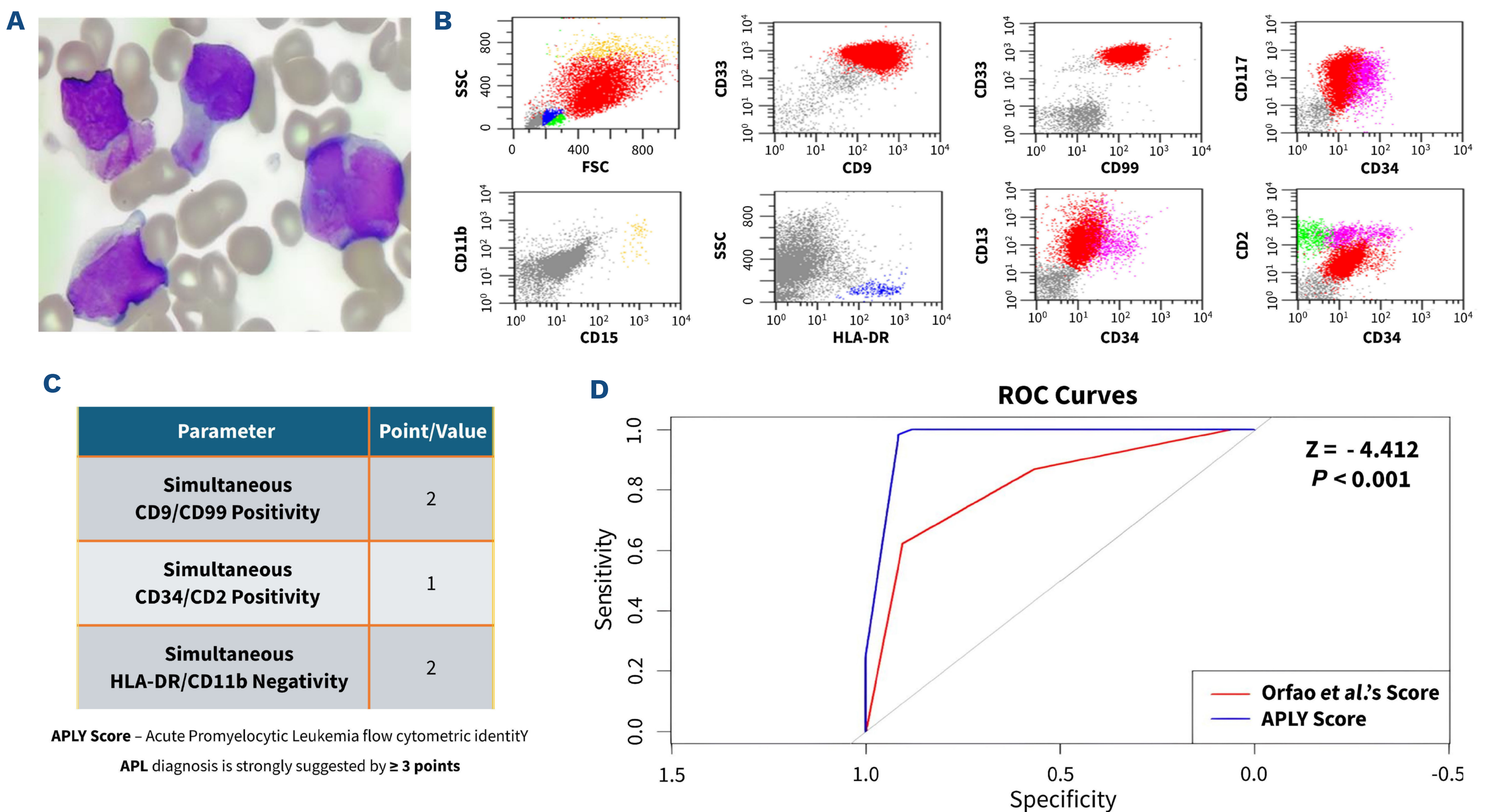
Rapid and accurate identification of acute promyelocytic leukemia with a novel multiparametric flow cytometric scoring system

Acute promyelocytic leukemia (APL) is usually characterized by the distinctive balanced chromosomal translocation t(15;17)(q22;q21), generating the pathogenic PML::RARα oncoprotein.[1] All-*trans* retinoic acid (ATRA)-based combinations therapies represent the cornerstone of APL treatment, making APL the acute myeloid leukemia (AML) subtype with the highest cure rate.[2] Nevertheless, APL remains a hematological emergency due to its life-threatening coagulopathy and high rate of early death, with nearly 35% of APL patients dying before the first ATRA administration.[3] Therefore, rapid and accurate diagnosis is essential, ideally within 24 hours of clinical suspicion. Morphological examination of peripheral blood and/or bone marrow smears represents the initial step to raise suspicion of APL. In fact, current guidelines strongly recommend initiating ATRA therapy immediately upon morphological APL suspicion to significantly reduce the risk of early death. Additionally, the use of anti-PML immunofluorescence assays has been proposed as a rapid and reliable alternative for the APL diagnosis. However, nowadays, in almost every center definitive diagnosis relies on detection of the *PML::RARA* fusion transcript by reverse transcriptase-polymerase chain reaction. Nevertheless, molecular and/or cytogenetic assays may take up 3 to 7 days, are potentially inconclusive (especially in variant/cryptic rearrangements), or are not available in all centers. Thus, multiparametric flow cytometry (MFC) remains an essential, routinely used tool for a rapid and accurate diagnostic workup of acute leukemias. Albeit many publications have reported a typical MFC-profile for APL leukemic cells,[4] not all cases consistently conform to this typical pattern,[5] prompting efforts to identify MFC marker combinations that maximize APL diagnostic accuracy. The most enduring and influential scoring system to predict the *PML::RARA* rearrangement remains Orfao *et al.*'s 1999 model.[6]

In this retrospective study, we evaluated MFC data of 158 consecutive newly diagnosed APL cases of the Hematology Department of "Sapienza"-University of Rome over a 27-year period (1997-2024), using an extensive flow cytometry panel. Bone marrow cells were stained using a combination of monoclonal antibodies recommended by the EuroFlow Consortium and by European LeukemiaNet guidelines:[7,8] MPO/cCD79a/cCD3/CD45/CD34/CD117/HLADR/CD13/CD33/CD11b/CD15/CD2/CD99/CD9/CD14/CD4/CD56/CD123/CD65/CD133/CD16/CD19/CD38/CD5/CD7 (Società Italiana Chimici, SIC, Life Sciences, Rome, Italy; Becton Dickinson, San Jose, CA, USA; Beckman Coulter, Brea, CA, USA) (Figure 1A, B). A positivity cutoff for CD34 of 10% was used.[9] Written informed consent was obtained according to local practice. All patients provided consent to treatment and to the use of their anonymized clinical data for scientific purposes. The study was conducted in accordance with the principles of the Declaration of Helsinki and complied with Italian ethical regulations. As a retrospective analysis using routinely collected clinical data, and in accordance with local regulations, formal approval from an ethics committee was not required. The mean age at diagnosis was 53 years (standard deviation, ±18 years) and 77 patients (49%) were male. A total of 38 patients (24%) were considered as morphological microgranular APL variants. Overall median expression percentages and positivity rates are displayed in the *Online Supplementary Table S1*. CD9, CD99, CD13, CD33, CD38 and MPO were constantly detected, with high median expression percentages and mean fluorescence intensities (MFI). CD117 resulted positive in 98% of APL samples. CD33 was expressed with a homogenous pattern in all 158 APL cases (100%), with a higher MFI compared to CD13, while CD13 had an heterogenous pattern of expression in 155 (98%). Conversely, CD11b, CD14 and CD65 were uniformly negative in all cases of APL, with HLA-DR and CD15 positive only in seven (4%) and four (3%) cases, respectively. CD34 resulted positive in 48 cases (30%) and positivity for CD2 was observed in 42 samples (27%), with most CD34$^+$ cases that were CD2$^+$ as well. CD9 and CD99 showed perfect flow cytometric correlation (P=1.0), as well as CD13 with CD33 (P=1.0), suggesting co-expression patterns among specific antigen pairs. Notably, moderately strong correlation was also observed between CD34 and CD2 (P=0.79), indicating their coordinated expression in a subset of cases. In fact, their contemporary positivity (CD34$^+$/CD2$^+$) was evidenced in 29 of 38 morphologically variant APL cases (76%) (*data not shown*).

Considering CD99 as a novel and promising marker for acute leukemias workup,[10] we selected 61 APL cases with available CD99 measurements and compared them to 97 consecutive newly diagnosed non-APL AML cases analyzed with comparable MFC panels over the 2014-2024 period (Table 1). The molecular and cytogenetic profile of the non-APL AML cohort included 21 patients with isolated *FLT3*-internal tandem duplication (ITD) mutations (21.6%), four with concurrent *FLT3*-ITD and *NPM1* mutations (4.1%), four with solely *NPM1* mutations (4.1%), 12 cases (12.4%) with complex karyotypes, four with inv(16)/t(16;16) (4.1%), and two (2.1%) patients with *KMT2A* alterations, one *KMT2A* rearrangement [t(9;11)(p21;q23)] (1.0%) and one *KMT2A*-PTD (1.0%), respec-



Parameter	Point/Value
Simultaneous CD9/CD99 Positivity	2
Simultaneous CD34/CD2 Positivity	1
Simultaneous HLA-DR/CD11b Negativity	2

Figure 1. Morphologic, immunophenotypic characterization and Acute Promyelocytic Leukemia flow cytometric identitY (APLY) score of acute promyelocytic leukemia cases. (A) Bone marrow smear morphology demonstrates abnormal promyelocytes with characteristic acute promyelocytic leukemia (APL) features, including abundant Auer rods and "Faggot" cells (1,000x magnifica-tio). (B) Flow cytometry dot plots illustrate the immunophenotype of the abnormal APL population (in red). Partial CD34/CD2 co-expression on APL blast cells is displayed in fuchsia. Residual granulocytes are marked in yellow, residual T lymphocytes in green, and residual B lymphocytes in blue. (C) Acute Promyelocytic Leukemia flow cytometric identitY (APLY) score parameters and their assigned points used to identify APL cases based on immunophenotypic features. A score ≥3 strongly suggests APL diagnosis. (D) Receiver operating characteristic (ROC) curve analysis of the APLY score (blue line) for the diagnosis of APL. The area under the curve (AUC) was 0.968 (95% confidence interval [CI]: 0.925-0.998), pinpointing an excellent discriminatory ability of the APLY score for the detection of *PML::RARA* fusion gene positivity. ROC analysis was used to determine the optimal cutoff value to discriminate *PML::RARA*-positive cases, balancing both sensitivity and specificity. ROC analysis was also performed for the Orfao *et al.*'s score, which showed a lower AUC of 0.816 (95% CI: 0.685-0.947). The DeLong test demonstrated a statistically significant difference between the 2 curves (Z=-4.412; *P*<0.001), confirming that the APLY score provides additional and clinically relevant diagnostic value compared to the reference Orfao *et al.*'s score. SSC: side scatter; FSC: forward scatter.

tively. Among the remaining cases, most exhibited a normal karyotype, while eight cases (8.3%) showed various recurrent chromosomal abnormalities. Various antigens expressions dissimilarities emerged between APL and non-APL cohorts (Table 1). Therefore, several differences in MFC antigen positivity between APL and non-APL cases emerged from the univariate analysis (*Online Supplementary Table S2*). To enhance discriminatory power, we evaluated co-expression patterns of some MFC antigens. Multivariate analysis identified that the three significant antigen pairs to discriminate between APL and non-APL diagnosis were: simultaneous CD9/CD99 positivity (odds ratio [OR] =58.71; 95% confidence interval [CI]: 5.82-8038.15; *P*<0.001), simultaneous CD34/CD2 positivity (OR=16.08; 95% CI: 1.47-389.78; *P*=0.022), and simultaneous HLA-DR/CD11b negativity (OR=38.78; 95% CI: 7.57-401.44; *P*<0.001) (Table 2). Thus, a weighted MFC diagnostic system score was developed, assigning differential point values to each of these three variables based on their OR. This score was named APLY (Acute Promyelocytic Leukemia flow cytometric identitY) and attributed two points to CD9/CD99 positivity and to HLA-DR/CD11b negativity and one point to CD34/CD2 positivity (Figure 1C). Based on the receiver operating characteristic (ROC) curve analysis, a cutoff of 3 was selected to discriminate between APL and other AML subtypes (Figure 1D). All 61 APL cases (100%) had a score ≥3, while only 11 of 97 non-APL cases (11.3%) reached this threshold (*P*<0.001) (*Online Supplementary Table S3*). These 11 non-APL cases, wrongly classified as APL by APLY score, exhibited heterogeneous molecular and cytogenetic profiles without a shared genetic signature, indicating that misclassification likely resulted from overlapping immunophenotypic features. Therefore, the APLY score achieved a sensitivity of 100.0% and a specificity of 88.4% for predicting an APL diagnosis. Its positive predictive value

Table 1. Overall multiparametric flow cytometry antigen expression and mean fluorescence intensity in all acute myeloid leukemia cases with available CD99 data.

A. Median expression percentage and median mean fluorescence intensity (MFI) in all selected acute myeloid leukemia (AML) cases and comparison between acute promyelocytic leukemia (APL) and non-APL AML.

	CD99% median (range)	CD99 MFI median (range)	CD9% median (range)	CD9 MFI median (range)	CD34% median (range)	CD2% median (range)	CD11b% median (range)	HLA-DR% median (range)	CD33% median (range)	CD33 MFI median (range)	CD13% median (range)	CD13 MFI median (range)	CD56% median (range)	CD38% median (range)	CD117% median (range)	CD133% median (range)	MPO% median (range)	CD4% median (range)	CD16% median (range)	CD15% median (range)
Total N=158	100 (0-100)	63 (2-392)	100 (0-100)	80 (2-1,254)	13 (0-100)	0 (0-100)	0 (0-100)	28 (0-100)	100 (0-100)	237 (5-2,641)	100 (0-100)	285 (15-1,800)	0 (0-100)	100 (63-100)	100 (1-100)	1 (0-100)	100 (0-100)	35 (0-100)	0 (0-19)	0 (0-100)
APL N=61	100 (97-100)	100 (42-392)	100 (100-100)	394 (51-1,254)	1 (0-100)	0 (0-100)	0 (0-0)	0 (0-28)	100 (68-100)	380 (38-2,641)	100 (69-100)	307 (42-113)	0 (0-77)	100 (100-100)	100 (26-100)	0 (0-100)	100 (100-100)	0 (0-100)	0 (0-0)	0 (0-10)
Non-APL AML N=97	100 (0-100)	39 (2-392)	25 (0-100)	26 (2-380)	55 (0-100)	0 (0-100)	0 (0-100)	100 (0-100)	100 (0-100)	155 (5-750)	100 (0-100)	235 (15-1,800)	0 (0-100)	100 (63-100)	100 (1-100)	100 (0-100)	48 (0-100)	84 (0-100)	0 (0-19)	0 (0-100)
P	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	0.12	<0.001*	0.11	0.28	<0.001*	0.17	0.15	<0.001*	<0.001*	<0.001*	0.43	<0.001*

*Statistically significant differences.

B. Antigen positivity rates and comparison between APL and non-APL AML.

	CD99 N (%)	CD9 N (%)	C34 N (%)	CD2 N (%)	CD11b N (%)	HLA-DR N (%)	CD33 N (%)	CD13 N (%)	CD56 N (%)	CD38 N (%)	CD117 N (%)	CD133 N (%)	CD65 N (%)	CD14 N (%)	MPO N (%)	CD7 N (%)	CD4 N (%)	CD16 N (%)	CD15 N (%)
Total N=158																			
Neg	36 (23)	45 (28)	73 (46)	135 (87)	136 (88)	77 (49)	2 (1)	4 (3)	135 (85)	0 (0)	9 (6)	81 (64)	132 (96)	131 (85)	19 (12)	131 (83)	71 (45)	155 (100)	132 (85)
Pos	122 (77)	113 (72)	85 (54)	21 (13)	19 (12)	81 (51)	156 (99)	154 (97)	23 (15)	157 (100)	149 (94)	45 (36)	5 (4)	23 (15)	139 (88)	27 (17)	86 (55)	0 (0)	23 (15)
Unknown	0	0	0	2	3	0	0	0	0	1	0	32	21	4	0	0	1	3	3
APL N=61																			
Neg	0 (0)	0 (0)	40 (66)	43 (70)	61 (100)	60 (98)	0 (0)	0 (0)	57 (93)	0 (0)	0 (0)	60 (98)	59 (100)	61 (100)	0 (0)	59 (97)	48 (79)	61 (100)	61 (100)
Pos	61 (100)	61 (100)	21 (34)	18 (30)	0 (0)	1 (2)	61 (100)	61 (100)	4 (7)	60 (100)	61 (100)	1 (2)	0 (0)	0 (0)	61 (100)	2 (3)	13 (21)	0 (0)	0 (0)
Unknown	0	0	0	0	0	0	0	0	0	1	0	0	2	0	0	0	0	0	0
Non-APL AML N=97																			
Neg	36 (37)	45 (46)	33 (34)	92 (97)	75 (80)	17 (18)	2 (2)	4 (4)	78 (80)	0 (0)	9 (9)	21 (32)	73 (94)	70 (75)	19 (20)	72 (74)	23 (24)	94 (100)	71 (76)
Pos	61 (63)	52 (54)	64 (66)	3 (3)	19 (20)	80 (82)	95 (98)	93 (96)	19 (20)	97 (100)	88 (91)	44 (68)	5 (6)	23 (25)	78 (80)	25 (26)	73 (76)	0 (0)	23 (24)
Unknown	0	0	0	2	3	0	0	0	0	0	0	32	19	4	0	0	1	3	3
P	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	0.69	0.28	0.042*	>0.95	0.036*	<0.001*	0.36	<0.001*	<0.001*	<0.001*	<0.001*	>0.95	<0.001*

*Statistically significant differences. Pos: positive; Neg: negative.

Table 2. Univariate and multivariate analyses of multiparametric flow cytometry antigen combinations for their significance in the differential diagnosis of acute promyelocytic leukemia.

Characteristics	Univariate analysis				Multivariate analysis	
	APL cases, N (%) N=61	Non-APL AML cases, N (%) N=97	OR (95% CI)	*P*	OR (95% CI)	*P*
Simultaneous CD34/CD2 positivity	17/61 (27.9)	3/97 (3.1)	9.58 (3.18-38.06)	<0.001	16.08 (1.47-389.78)	0.022*
Simultaneous CD9/CD99 positivity	61/61 (100.0)	34/97 (35.0)	226.39 (30.85-2,888.01)	<0.001	58.71 (5.82-8,038.15)	<0.001*
Typical CD34/CD15 pattern	42/61 (68.9)	21/97 (21.6)	7.75 (3.85-16.26)	<0.001	4.44 (0.74-27.27)	0.10
Simultaneous HLA-DR/CD11b negativity	60/61 (98.3)	15/97 (15.5)	214.68 (51.84-1,993.64)	<0.001	38.78 (7.57-401.44)	<0.001*
Simultaneous CD13-heterogeneous and CD33-homogeneous pattern	58/61 (95.0)	64/97 (66.0)	8.68 (3.08-33.27)	<0.001	3.56 (0.46-27.46)	0.21

In multivariate analysis **P* values are statistically significant. APL: acute promyelocytic leukemia; AML: acute myeloid leukemia; OR: odds ratio; CI: confidence interval.

(PPV) was 84.7% and the negative predictive value (NPV) was 100%, with a consequent optimal F1 score of 91.8%. Subsequently, we applied on our population the historical and world-wide acknowledged Orfao *et al.*'s score with a score of 3 suggesting an APL diagnosis. Thirty-eight of 61 APL cases (62%) and nine of 97 non-APL cases (9%) reached this cutoff, yielding a sensitivity of 62.3% and a specificity of 90.5% (*Online Supplementary Table S3*). In our cohort, the comparison with this pivotal model showed that sensitivity was higher for the APLY score (100.0% *vs.* 62.3%) ($P<0.001$), with no meaningful difference in specificity (88.4% *vs.* 90.5%) ($P=0.64$). Similarly, the F1 score was significantly superior (0.92 *vs.* 0.70) ($P<0.001$), highlighting the improved overall classification performance. Moreover, C-index was higher for the APLY score (C-index=0.967; 95% CI: 0.925-0.998 *vs.* C-index=0.816; 95% CI: 0.685-0.947), and the DeLong test demonstrated a highly significant difference between the area under the curve (AUC) (Z=-4.412; $P<0.001$) (Figure 1D). The Net Reclassification Improvement (NRI) was 0.356, indicating that 35.6% of patients were more accurately classified by the APLY score, with 23 APL cases correctly reclassified (37.7%) and only two non-APL cases incorrectly reclassified as APL (2.1%) compared to the Orfao *et al.*'s score.

Delay in timely treatment is the main factor affecting the APL survival rate. Albeit molecular testing remains the gold-standard for APL diagnosis, rapid turnaround MFC data may support the prompt initiation of life-saving therapy. In this study, we demonstrated that APL cases could be rapidly and accurately identified by MFC using routine screening panels and we proposed a novel MFC scoring system (APLY score) for APL diagnosis. Our study emphasizes that CD9 and CD99 are always strongly expressed by all APL leukemic cells. While previous studies have revealed that nearly all APL samples (95-100%) exhibit homogeneous and moderate/bright expression of CD9,[11,12] to our best knowledge, our report represents the first study showing that CD99 and CD9 shares a uniform expression pattern in APL cases. In our APL cohort, CD99 was uniformly expressed on leukemic blasts and showed perfect concordance with CD9 ($P=1.0$). Consequently, we assessed CD9 and CD99 as a dual-antigen MFC signature ($CD9^+/CD99^+$) to improve diagnostic specificity. CD11b negativity in myeloid cells is a well-documented flow cytometric hallmark of APL.[12] Likewise, APL blasts characteristically often lack HLA-DR expression.[13] However, because isolated CD11b negativity or HLA-DR absence are not entirely specific for APL diagnosis, in our study we evaluated their simultaneous negativity to enhance APL diagnostic confidence. We found that this dual-negative ($HLA\text{-}DR^-/CD11b^-$) signature in 98.3% of APL cases compared to just 15.5% of non-APL cases, closely mirroring Dong *et al.*'s report of 96% and 13%, respectively.[13] Although CD34 have been historically considered negative in APL cases over time studies have demonstrated that up to 20-40% of APL cases may exhibit CD34.[5] Moreover, CD34 expression in APL has been almost invariably associated with concurrent aberrant expression of CD2. This dual positivity ($CD34^+/CD2^+$) is more commonly observed in the microgranular APL variant. In our cohort, 28% of APL cases exhibited simultaneous $CD34^+/CD2^+$ expression, with a markedly higher frequency observed among cases with a variant morphology (76%). Similarly, Albano *et al.* reported that among morphologic variants, approximately 50-60% displayed a $CD34^+/CD2^+$ expression pattern.[14] Thus, the evaluation of $CD34^+/CD2^+$ expression and its inclusion into the APLY score enhances the identification of APL variant cases, since this positivity combination is anecdotal in non-APL AML. Therefore, in cases showing atypical or borderline immunophenotypic features, the APLY score seems

to substantially reduce diagnostic uncertainty, along with historical parameters such as high side scatter, and the homogeneous *versus* heterogeneous expression patterns of CD33 and CD13, respectively.

Therefore, our results show that the combined use of three flow cytometric dual-antigen evaluations (CD9$^+$/CD99$^+$, CD34$^+$/CD2$^+$ and HLA-DR$^-$/CD11b$^-$) in a diagnostic MFC score (APLY score) yield excellent diagnostic performance, with an optimal sensitivity (100.0%) and specificity (88.4%) for discriminating those newly diagnosed AML cases in which molecular investigation to detect *PML::RARA* fusion rearrangements should promptly be performed. Remarkably, the APLY score (a straightforward, easy-to-apply scoring system), employing simple markers that should be accessible in any flow cytometry laboratory, correctly identified all APL cases in our cohort, underscoring its reliability as a front-line screening tool to facilitate the prompt ATRA administration as per clinical guidelines.[15] In particular, in peripheral centers or developing countries, where rapid molecular diagnosis of APL may be challenging, the APLY score could be a valuable robust screening tool considering that the required monoclonal antibodies are widely accessible and suitable for evaluation with whichever type of cytometer available to date, supporting the reproducibility of this approach across different laboratory settings. Moreover, the comparison with the historical Orfao *et al.*'s score[6] enabled to demonstrate that the inclusion of new and simple markers (such as CD99, CD9, CD2 and CD11b) yields a more accurate predictability of *PML::RARA* rearrangement and may be more easily applicable in routine clinical settings, requiring less expertise in MFC analysis and interpretation. External validation studies may further confirm these findings to integrate the APLY score into routine AML diagnostic workflows.

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Contributions

AL wrote the manuscript. DF and DK contributed to flow cytometry data. CAG and FN contributed to laboratory work. MGN assisted with laboratory work and complementary exams. ES, IC, MLB and CM followed the patients. MLM contributed to the collection and acquisition of flow cytometry data. CI and SB analyzed molecular data. MZL performed and analyzed cytogenetic tests. DD analyzed and interpreted molecular data. MM and MB revised the manuscript and accepted the final version. MSDP conceptualized, revised and approved the final version of the manuscript. All authors have read and agreed to the published version of the manuscript.

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Data-sharing statement

The data that support the findings of this study are available in the text and from the corresponding author, Massimo Breccia, upon reasonable request.

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