PEARL SCORE AND SINGLE-CELL TRANSCRIPTOMIC PROFILING REVEAL CLINICAL AND MOLECULAR DETERMINANTS OF EARLY DEATH IN ACUTE PROMYELOCYTIC LEUKEMIA

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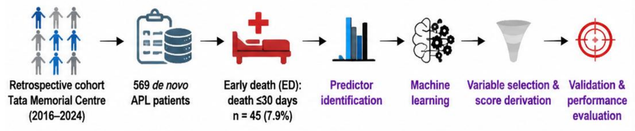
BACKGROUND & OBJECTIVES

- APL is highly curable with ATRA/ATO, but early death (<30 days) remains the major barrier of cure (~8-20%).
- Hemorrhagic coagulopathy is the leading cause of early death.
- Existing risk scores (Sanz, Cai, osterroos, and EASIX) rely on limited parameters and have modest predictive performance.
- Cellular and transcriptional programs underlying hemorrhagic heterogeneity in APL remains poorly defined.

OBJECTIVES

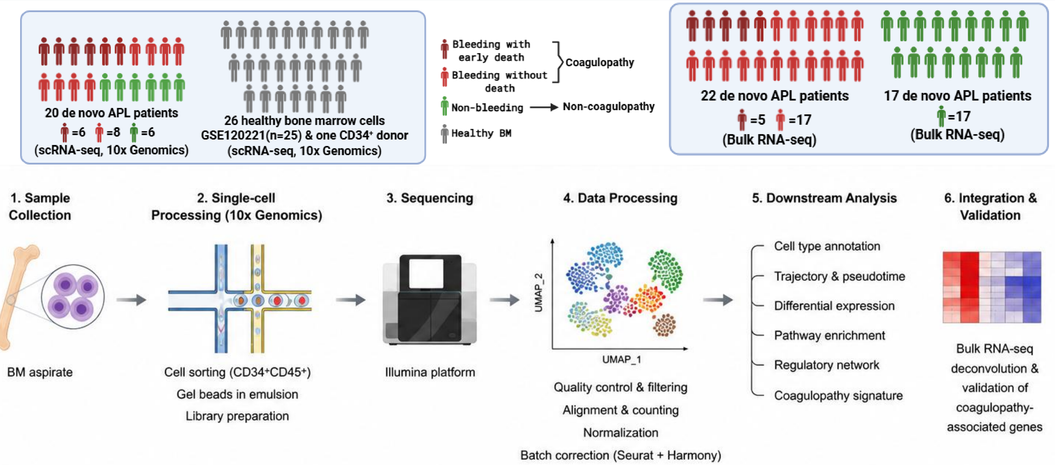
1. Develop and validate a simple clinical risk score for early death using routinely available laboratory parameters.
2. Identify single-cell transcriptional programs and cellular heterogeneity associated with APL coagulopathy-related early death

METHODS: STUDY DESIGN & ANALYTICAL PIPELINE

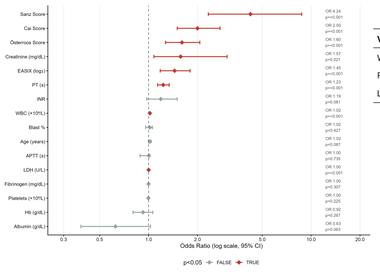


569 APL patients | ED = 45 (7.9%)	
Median age (IQR)	34 (22–44) | 35 (28–46)
Male / Female (%)	59% / 41% | 64% / 36%
High-risk (Sanz)	46% overall | 82% in ED
Bleeding at presentation	72% overall | 93% in ED
Median WBC (×10⁹/L)	9 (3–30) | 58 (14–93)
Median PT (s)	17.0 (14.9–19.4) | 19.7 (18.0–22.4)
Median LDH (U/L)	351 (243–564) | 654 (344–1,103)
Creatinine (mg/dL)	0.80 (0.60–0.93) | 0.80 (0.70–1.06)

Firth logistic regression (univariate & multivariate) → Machine learning models (XGBoost / Elastic Net / Random Forest) → Cross-validation & Bootstrap selection → Score (PEARL) creation → Validation → Performance evaluation



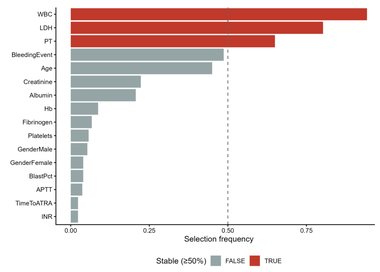
1. Key Univariate Predictor of early Death (Firth Logistic Regression)



2. Multivariate analysis

Variable	Adjusted OR (95% CI)	p-value
WBC (×10⁹/L)	1.02 (1.01–1.02)	<0.001
PT (seconds)	1.12 (1.01–1.26)	0.030
LDH (U/L)	1.00 (1.00–1.00)	0.035

3. Variable Stability: Bootstrap LASSO (300 Bootstrap)



4. PEARL Score Construction

Variable	Cutpoint	Direction	Points
WBC (×10⁹/L)	39.2	≥	2
LDH (U/L)	521.5	≥	1
PT (seconds)	18.8	≥	2

SCORING RULE
Assign points if the value is **greater than or equal to** the cutpoint.
Total PEARL Score = Sum of points (Range: 0 – 5)

RISK CATEGORIES BASED ON PEARL SCORE

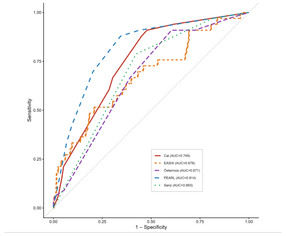
LOW RISK (0 point)	INTERMEDIATE RISK (1–2 points)	HIGH RISK (≥3 points)
ED rate 1.0%	ED rate 7.1%	ED rate 21.7%

DISTRIBUTION OF PATIENTS AND EARLY DEATH BY PEARL RISK GROUP

PEARL_Risk	N	ED_n	ED_pct
Low (0)	299	3	1.0%
Intermediate (1–2)	113	8	7.1%
High (≥3)	157	34	21.7%

5. AUC ROC Comparison (n=359, ED=33*)

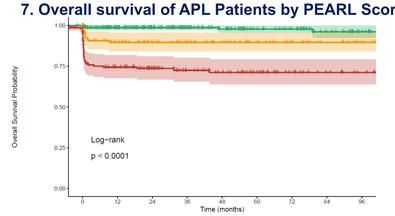
*Patients with available data for all scores



6. Performance of Early Death Risk Scores in APL

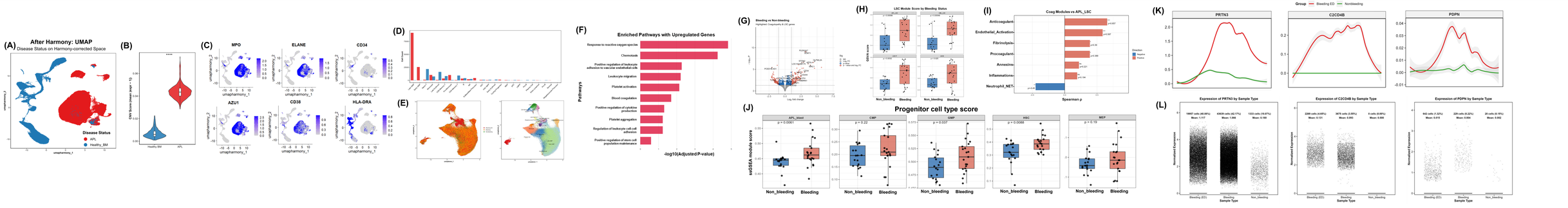
Score	Variables	N available	AUC	Bootstrap-corrected AUC	Fixed cutoffs
PEARL (ML-derived)	WBC, LDH, PT	569	0.823	0.759	Yes
Sanz	WBC, Platelets	569	0.710	–	Yes
Cai	Age, WBC, Platelets, LDH	359	0.749	–	Yes
Österroos	Age, WBC, Platelets	569	0.676	–	Yes
EASIX (log_2)	LDH, Creatinine, Platelets	359	0.678	–	No

7. Overall survival of APL Patients by PEARL Score



Number at risk

Low (0)	296	224	179	136	110	85	75	54	37
Intermediate (1–2)	112	84	67	55	45	32	21	13	6
High (≥3)	150	100	77	59	50	37	23	14	8



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