Durable Complete Remission Following HMA Therapy in Higher-Risk MDS Is Not Fully Determined by Baseline Disease Biology

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BACKGROUND:

- Complete remission (CR) rates are commonly used to assess efficacy in higher-risk myelodysplastic syndromes (HR-MDS), yet CR does not consistently translate into durable clinical benefit. [1-4]
- We previously demonstrated that durable CR (CR ≥6 months) is a stronger surrogate endpoint for overall survival than CR alone in HR-MDS.

AIM:

- We aimed to evaluate whether achieving a durable CR can be predicted using baseline clinical and molecular characteristics.

METHODS:

Statistical Workflow

- **983 HR-MDS patients**
- **Primary endpoint:** CR ≥6 months (CR6)
- **Baseline predictors:** demographics, hematologic variables, cytogenetics, *TP53*, VAF, recurrent myeloid mutations (Splicing mutations, *ASXL1, EZH2, RUNX1*)
- **Primary analysis:** Multivariable logistic regression
- **Outputs:** Adjusted ORs, 95% CIs, P values
- **Model discrimination:** ROC curve and AUC
- **Sensitivity analysis:** Gradient boosting
- **Validation:** Stratified 5-fold cross-validation

CONCLUSIONS

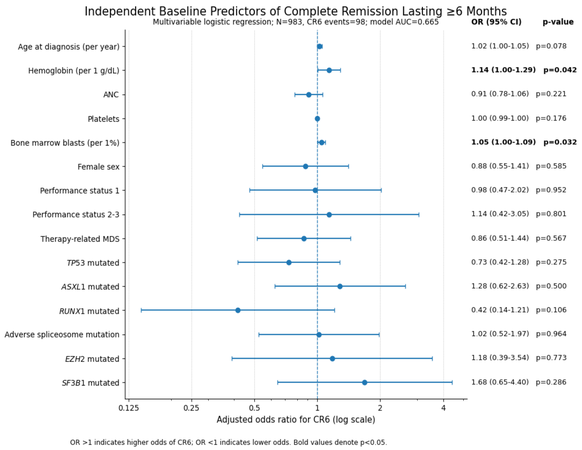
- Across both traditional statistical modeling and machine learning approaches, pretreatment molecular and clinical characteristics were insufficient to accurately identify patients who would achieve durable CR.
- This suggests that durable remission reflects treatment-responsive disease biology that is not fully captured by pretreatment features.
- These findings suggest that biomarkers reflecting dynamic treatment response rather than static pretreatment characteristics may better identify patients capable of achieving durable remission.

RESULTS

Variable	CR<6 months (N=13)	CR≥6 months (N=98)	p-value
Age, years	73.8 (71.7–78.7)	74.4 (69.1–78.3)	0.512
Hemoglobin, g/dL	9.1 (7.7–9.6)	9.4 (8.4–10.4)	0.274
Platelet count, ×10^9/L	57.0 (27.0–91.0)	70.0 (36.0–104.2)	0.347
ANC, ×10^9/L	0.8 (0.3–1.4)	0.9 (0.5–1.4)	0.371
Bone marrow blasts, %	11.0 (7.0–14.0)	10.0 (6.0–14.0)	0.607
IPSS-M high/very high	6 (100.0%)	41 (78.8%)	0.583
Therapy-related MDS	3 (23.1%)	25 (25.5%)	1.000
AML transformation	5 (38.5%)	51 (52.0%)	0.358
RBC transfusion dependence	7 (53.8%)	46 (46.9%)	0.639
Platelet transfusion dependence	4 (30.8%)	29 (29.6%)	1.000
Complex cytogenetics	7 (53.8%)	44 (46.8%)	0.634
TP53 mutation	2 (33.3%)	21 (38.2%)	1.000
RAS mutation	0 (0.0%)	3 (5.8%)	1.000
SRSF2 mutation	0 (0.0%)	5 (9.6%)	1.000
ZRSR2 mutation	0 (0.0%)	2 (3.8%)	1.000
U2AF1 mutation	1 (16.7%)	7 (13.5%)	1.000
EZH2 mutation	0 (0.0%)	3 (5.5%)	1.000
ASXL1 mutation	1 (16.7%)	12 (21.8%)	1.000
IDH1 mutation	1 (16.7%)	2 (3.8%)	0.279
IDH2 mutation	0 (0.0%)	1 (1.9%)	1.000

Baseline Patient and Disease Characteristics (N=980)

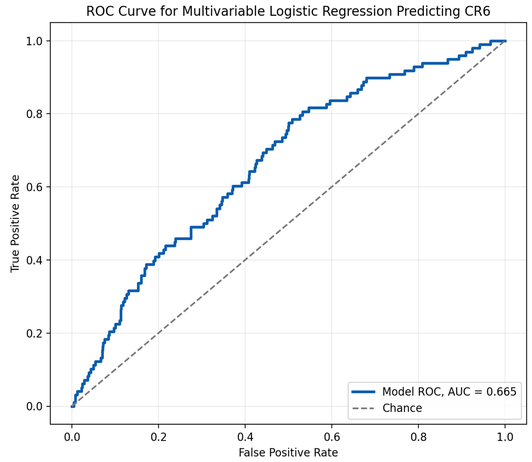
Key Findings:
- Only hemoglobin and bone marrow blast percentage independently predicted durable CR.
- Neither *TP53* mutation status nor *TP53* VAF independently predicted response.
- Baseline pretreatment variables demonstrated only modest predictive performance (AUC = 0.665).
- Concordant findings from logistic regression and gradient boosting suggest that durable CR is not fully explained by baseline disease biology.



OR >1 indicates higher odds of CR6; OR <1 indicates lower odds. Bold values denote p<0.05.

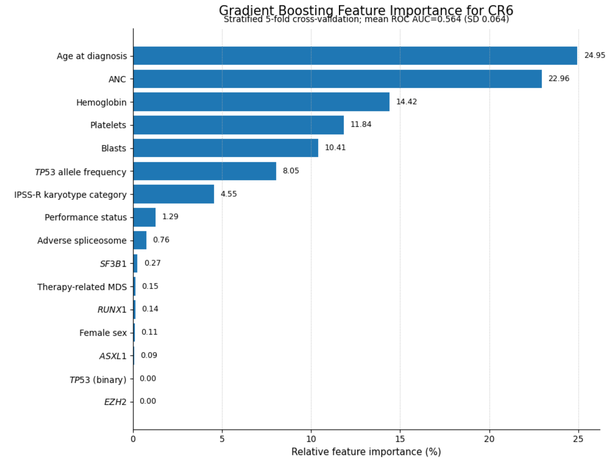
Adjusted Odds Ratios (95% CI) for Baseline Predictors of Durable CR

- Hemoglobin and bone marrow blast percentage were the only independent predictors of CR6.
- Baseline molecular features, including *TP53* mutation status and variant allele frequency, were not independently associated with durable response.



ROC Curve for the Multivariable Logistic Regression Model Predicting Durable CR

- Model discrimination was modest (AUC = 0.665), indicating that baseline variables explain only a limited proportion of durable CR.



Sensitivity Analysis: Gradient Boosting Predictors of Durable CR

- Gradient boosting produced findings concordant with the multivariable model, confirming that clinical variables carried most of the predictive information while molecular mutations contributed little incremental value.

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