Clinical and Prognostic Impact of CEBPA Mutations in Myelodysplastic Syndromes

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CEBPA-mutated MDS is a high-risk, transformation-prone subgroup; the AML bZIP-favorable paradigm does not translate to MDS.

2.7% of MDS carry a CEBPA mutation (n = 66 / 2,442)

17.2 vs 42.2 17.2 vs 42.2 months / median OS, CEBPA-mutated vs wild-type (HR 2.05; p<0.001)

44.0% 44.0% vs 19.5% / 36-month AML transformation (sHR 1.89; p=0.006)

BACKGROUND & OBJECTIVE

- In AML, biallelic CEBPA mutations (especially bZIP in-frame indels) define ELN 2022 Favorable risk, with 5-year OS ~60% after intensive induction.
- WHO 2022 retains the ≥20% blast threshold: CEBPA-mutated patients below it are classified as MDS and treated with hypomethylating agents. whether the AML-favorable biology applies is unknown.
- CEBPA mutations occur in 1–5% of MDS but have never been characterized as a dedicated subgroup; IPSS-M embeds CEBPA in a 15-gene residual term (Nres) with no gene-specific risk estimate.
- Does the AML bZIP-favorable paradigm translate to CEBPA-mutated MDS? — Define prognostic impact (OS, LFS, AML transformation), mutation-subtype biology, and co-mutation context in the IWG 2022 registry.

METHODS

- Study Population: IWG 2022 multi-center MDS registry (n=2,442 evaluable; WHO 2016); 66 CEBPA-mutated (2.7%)
- Endpoints: OS (primary), LFS (secondary). Median follow-up 45.9 mo.
- Kaplan-Meier and Cox proportional hazards regression.
- Cox models: A (CEBPA + age + sex) → B (Model A +IPSS-R) → co-mutation–adjusted.
- Competing risks evaluated via Fine-Gray sub distribution hazards (death without AML transformation as the competing event).
- MSK-IMPACT 2020 (n=977) for mutation characterization only — no survival data.

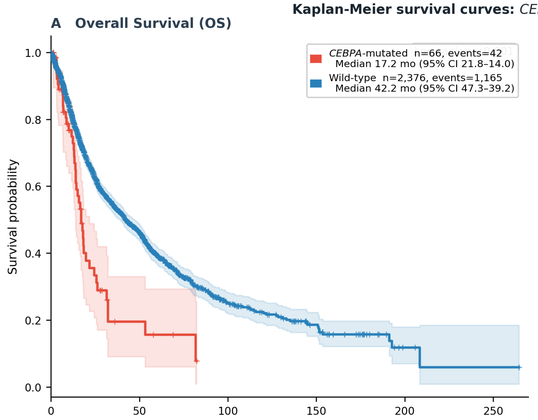
Results

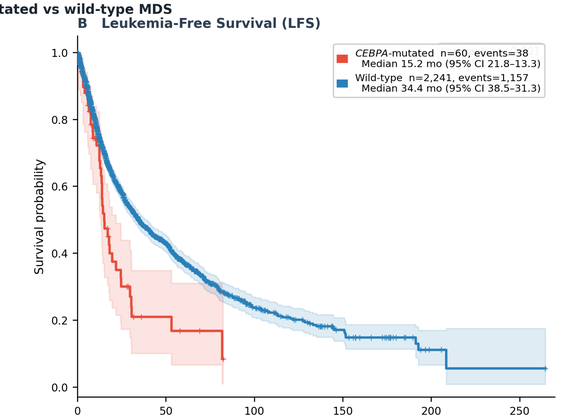
- Median OS 17.2 vs 42.2 months (HR 2.05, 95% CI 1.50–2.79; p<0.001); LFS 15.2 vs 34.4 months (HR 1.79; p<0.001).
- After IPSS-R adjustment, the association is borderline (HR 1.39; p=0.053). Co-mutation adjustment further attenuates the HR to 1.11, indicating the signal partially reflects an adverse co-mutational context (e.g., STAG2, ASXL1).

Table 1. Baseline characteristics by CEBPA mutation status

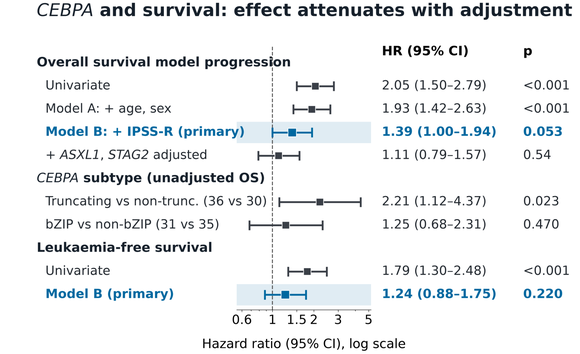
Characteristic	CEBPA-mutated (n=66)	Wild-type (n=2,376)	p
Age, median (IQR), yr	74.0 (67.0–77.0)	72.0 (63.0–78.0)	0.642
Male sex, n (%)	48 (72.7%)	1425 (60.0%)	0.050
BM blast %, median (IQR)	7.5 (3.5–11.5)	3.0 (1.0–7.0)	<0.001
WHO 2016: MDS-EB1, n (%)	16 (25.4%)	428 (18.4%)	<0.001
WHO 2016: MDS-EB2, n (%)	27 (42.9%)	399 (17.2%)	—
IPSS-R score, median (IQR)	4.5 (3.5–5.5)	3.0 (2.0–4.5)	<0.001
IPSS-M score, median (IQR)	1.4 (0.1–1.9)	-0.3 (-1.1–1.0)	<0.001
Complex karyotype, n (%)	1 (1.5%)	245 (10.3%)	0.033
Normal karyotype (within non-complex), n (%)	41 (69.5%)	1,159 (62.0%)	0.277

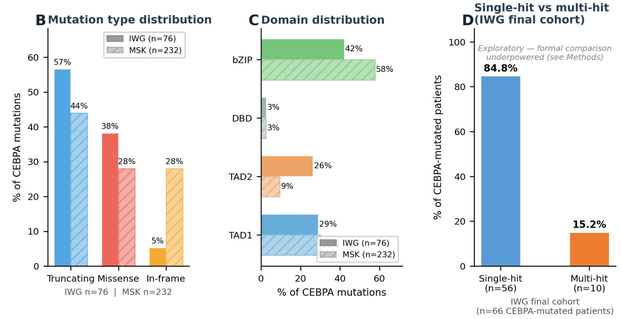
Kaplan-Meier survival curves: *CEBPA*-mutated vs wild-type MDS



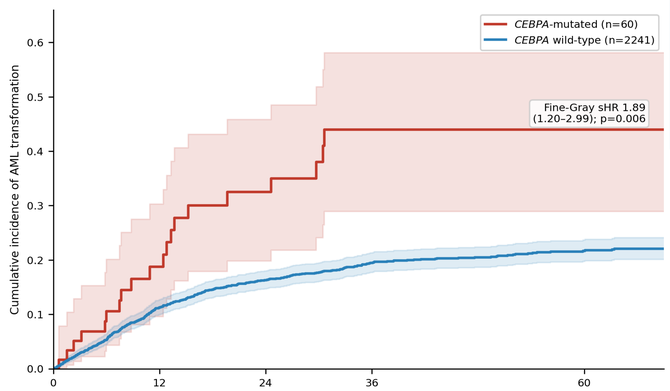


***CEBPA* and survival: effect attenuates with adjustment**





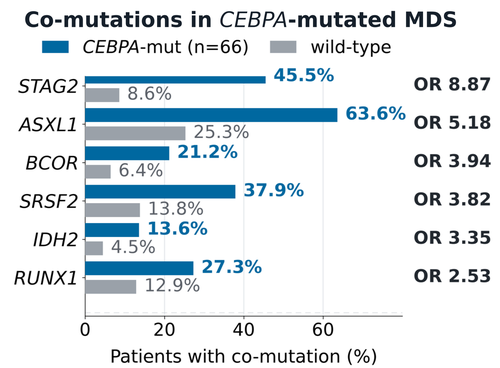
Cumulative incidence of AML transformation



- Cumulative AML transformation at 36 months: 44.0% vs 19.5%.
- Death without transformation: cause-specific HR 0.97 (p=0.89) — no excess non-leukemic mortality.
- 20 of 36 deaths in CEBPA-mutated patients occurred as AML transformation.

- Truncating mutations drive the signal
- bZIP involvement confers no benefit: multi-hit no better than single-hit.
- The AML-favorable subset — bZIP in-frame indels — was vanishingly rare: 2 of 66 patients.
- Transformation risk is class-level, not subtype-specific (truncating 42.4% vs 22.2%, p=0.17; bZIP 41.4% vs 25.8%, p=0.28)..

Co-mutations in *CEBPA*-mutated MDS



CONCLUSIONS

- CEBPA mutations mark a rare (2.7%) MDS subgroup with markedly inferior survival.
- Excess mortality is mediated through leukemic transformation, not accelerated non-transformative MDS death.
- Truncating loss-of-function mutations drive the signal.
- bZIP involvement confers no benefit. The AML bZIP-favorable paradigm does not translate to MDS and should not guide prognosis.

LIMITATIONS

- Primary adjusted HR 1.39 (95% CI 1.00–1.94; p=0.053) is borderline — 66 patients, 36 events.
- Co-mutation adjustment attenuates the HR to 1.11.
- No treatment data; bZIP chemosensitivity hypothesis untestable.
- No external survival validation (MSK cohort lacks survival endpoints).
- Retrospective and observational; associations are prognostic.

Full article (open access)

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