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Myelodysplastic Syndromes

VARIANT-SPECIFIC PROGNOSTIC IMPACT OF SRSF2 P95 MUTATIONS IN ASXL1-MUTATED MYELODYSPLASTIC SYNDROMES

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Background: Mutations in ASXL1 occur in approximately 20–30% of myelodysplastic syndromes (MDS) and are frequently associated with adverse prognosis. Among ASXL1--mutated MDS, SRSF2 represents one of the most recurrent co-mutations, affecting up to one-third of cases. SRSF2 mutations, particularly those involving codon P95, are known to alter splicing fidelity and drive myeloid transformation, but the clinical impact of specific SRSF2 variants within ASXL1-mutated MDS remains poorly defined.

Methods: We analyzed a multicenter cohort of 852 patients with ASXL1-mutated MDS, including 28.1% harboring SRSF2 mutations. Patients were drawn from four independent databases: the MDS Unit of Careggi University Hospital (Florence, Italy), the IPSS-M development cohort, the Cleveland Clinic MDS registry (Cleveland, USA), and the GenoMed4All project at IRCCS Humanitas Research Hospital (Milan, Italy). Eligible patients had a diagnosis of MDS according to the WHO 2022 classification and at least one pathogenic ASXL1 mutation. Clinical parameters, mutational profiles, and prognostic scores were compared between ASXL1mut/SRSF2wt and ASXL1mut/SRSF2mut groups. Survival outcomes were evaluated using Cox proportional hazards models adjusted for the continuous IPSS-M score.

Results: Patients with ASXL1mut/SRSF2mut displayed a more advanced disease phenotype at diagnosis, with higher bone marrow blasts (median 7.0% vs 4.0%, $p < 0.001$), lower neutrophil counts (1.09 vs 1.70 $\times 10^9$/L, $p < 0.001$), and higher IPSS-M scores (median 1.38 vs 0.23, $p < 0.001$). Within SRSF2-mutated cases (n = 234), hotspot distribution was as follows: p.P95H (58.1%), p.P95L (19.2%), p.P95_103del (10.7%), p.P95R (10.3%), and p.P95A (1.7%). Distinct co-mutational patterns emerged: U2AF1 (25%), TET2 (25%), and SF3B1 (18.8%) were most frequent in SRSF2wt cases, whereas STAG2 (42.6%), TET2 (35.7%), IDH2 (21.7%), and BCOR (10.2%) predominated in SRSF2mut patients. In multivariable analysis adjusted for IPSS-M (HR = 1.53; 95% CI 1.40–1.68; $p < 0.001$), SRSF2 variants exhibited heterogeneous prognostic effects compared with SRSF2 wild-type. The p.P95_102del and p.P95_103del variants were associated with significantly inferior overall survival (HR = 1.86; 95% CI 1.15–2.99; $p = 0.011$), whereas p.P95H conferred a reduced risk of death (HR = 0.70; 95% CI 0.53–0.92; $p = 0.011$) compared with SRSF2wt cases. Other variants (p.P95L, p.P95R, p.P95A) showed no significant differences.

Conclusions: In ASXL1-mutated MDS, SRSF2 co-mutation defines a distinct biological and clinical subset characterized by higher blast burden, specific co-mutational architecture, and worse baseline risk profile. Importantly, the prognostic impact of SRSF2 is variant-specific: deletion-type variants (p.P95_102del/p.P95_103del) identify patients with independently adverse outcomes, while p.P95H may be associated with a more indolent disease course. These findings highlight the need for variant-level annotation of SRSF2 mutations in future prognostic models and clinical decision-making.