Abstract: P738

Title: CLASSIFICATION AND PROGNOSTIC STRATIFICATION BASED ON GENOMIC FEATURES IN MYELOID DYSPLASTIC NEOPLASMS, MYELOPROLIFERATIVE NEOPLASMS AND THEIR OVERLAPPING CONDITIONS.

Abstract Type: Poster Presentation

Topic: Myelodysplastic syndromes - Biology & translational research

Background:

Recent genomic studies have offered an alternative paradigm for the classification of myeloid neoplasms (MNs), focusing on shared and distinct genomic patterns. Nevertheless, current frameworks still prioritize clinical features over biological characteristics in distinguishing major classes of MN.

Aims:

We advocate for genomic characterization through unsupervised genomic grouping using comprehensive cohort to refine and advance MN classification.

Methods:

Clinical and genomic data were collected from patients, who performed diagnostic NGS study targeting 87 genes for MN from 2017 to 2021. After exclusion of patients with non-targeting disease, or insufficient clinical data, 1,585 patients were included in the modeling. We applied Dirichlet process (DP) clustering to define genomic subgroups and assessed survival impact.

Results:

According to the 2022 WHO criteria, diagnosis of myeloproliferative neoplasm (MPN, n=715), myelodysplastic neoplasm (MDS, n=698), MDS/MPN (n=94) and their morphologically defined subtypes were determined. We also included patients with aplastic anemia (AA, n=94), who initially suspicious for MNs.

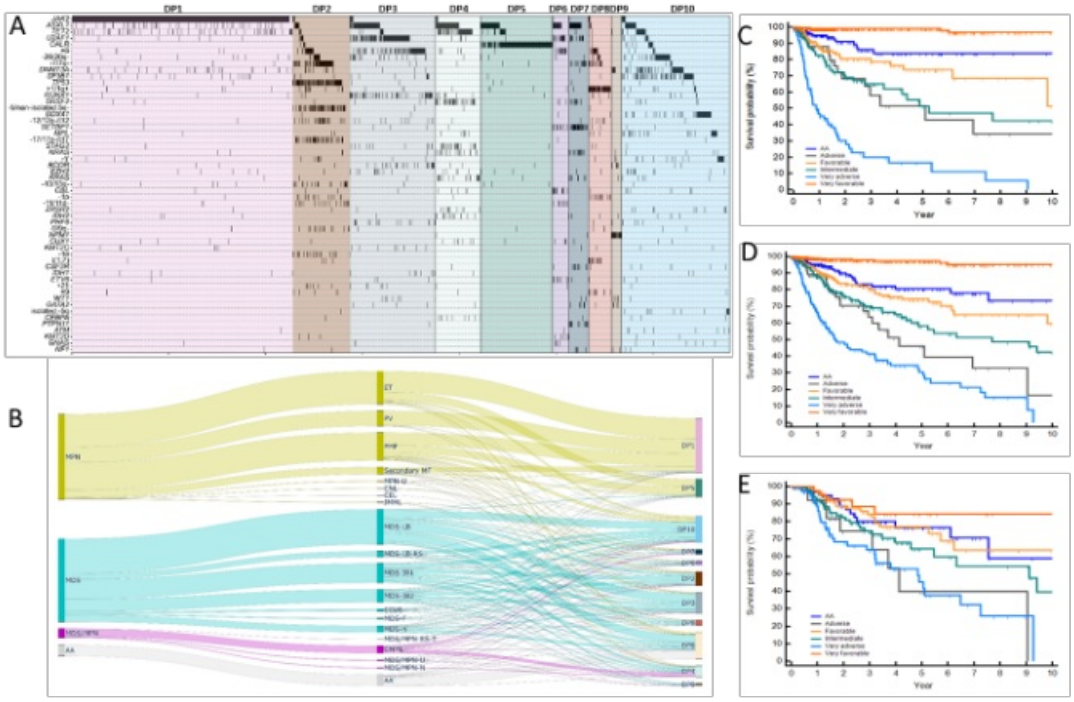
Through the application of the DP, we identified 10 distinct groups (Figure 1A), each characterized by unique genomic features, MN subtypes and risk categories (Figure 1B). For instance, DP1 (n=456) and DP5 (n=148) were predominantly MPN patients with *JAK2* and *CALR* mutation, respectively, while DP2 (n=118) featured MDS patients possessing *TP53* mutation and complex karyotypes. DP9 (n=21) was marked by AML related mutations including *NPM1*. In DP7 (n=40), patients with *SETBP1* mutation exhibited heterozygous phenotypes, such as MDS, CMML, PMF, CNL and JMML. DP4 (n=93), featured *TET2* and *SRSF2* mutations among patients with MDS and CMML. DP3 (n=117) was associated with *U2AF1, RUNX1, BCOR1* and *PHF6* mutations, and chromosomal changes such as +8. DP6 (n=35) was linked to *CBL, ETV6* and *KMT2D* mutations. DP3 and DP6 predominantly included patients diagnosed with MDS. DP10 (n=224), showed genomic heterogeneity, associated with mutations in *SF3B1* or *DDX41. DDX41* was totally exclusive to *SF3B1*, and majority of *DDX41* cases accompanied germline *DDX41* mutation. DP8 (n=47) was enriched with MDS patients possessing chromosome 1q abnormalities, especially der(1;7). Lastly, DP0 (n=226), which showed no genetic abnormalities, mostly consisted of patients diagnosed with AA and MDS-h.

Then, we stratified the 10 DP groups into six distinct risk categories, based on survival probabilities (Figure 1C). The *Very favorable MN*, comprising DP1 and DP5, showed an estimated survival of 15 years (95% CI: 10.9-12.3). In contrast, DP2, DP7 and DP9, categorized as *Very adverse MN* showed notably lower median survival of 1.7 years (1.3-9.3). DP4, classified as *Adverse MN* had median survival of 4.1 years (3.0-9.0). The *Intermediate MN*, encompassing DP3 and DP6, revealed a median survival year of 7.7 (4.9-10.7),*Favorable MN*, consisting of DP10 and DP8, exhibited a median survival year of 14.6 (9.8-17.7). Additionally, DP0, lacking specific genomic abnormalities, exhibited an estimated survival of 12.4 years (11.2-13.7). Notably, the established risk stratification for survival remained consistent among non-transplanted patients (Figure 1D), where the impact

of transplantation on survival was most pronounced *very adverse MN* (Figure 1E).

Summary/Conclusion:

This study provides valuable insights into the DP-driven genomic grouping in MNs, encompassing both well-established prognostic entities and those lacking clear prognostic guidelines. We elucidated the clinical relevance of specific mutations such as *TP53* and *NPM1*. Additionally, our findings highlight the need to reevaluate current risk stratification systems, particularly concerning mutations in *SETBP1*, *DDX41*, and chromosome 1q derivatives. This study suggests the importance of refining genomic group in MNs for potential implications in clinical management strategies.



Keywords: Myeloproliferative disorder, Genomics, MDS, Myelodysplastic syndrome