Clinical and Experimental Medicine

RESEARCH | Article in Press

Prognostic stratification in MDS/MPN syndromes other than CMML: an Italian multicenter real-world study

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Received: 14 July 2026 / Accepted: 3 August 2026

Abstract

MDS/MPN syndromes comprise a heterogeneous group of myeloid neoplasms. While CMML has been extensively characterized, data on other MDS/MPN entities remain limited, particularly in real-world settings. We conducted a nationwide, multicenter retrospective study including adult patients with MDS/MPN syndromes other than CMML from 17 Italian centers. Patients were classified as MDS/MPN with *SF3B1* mutation and thrombocytosis (*SF3B1*-T), atypical chronic myeloid leukemia/chronic neutrophilic leukemia (aCML/CNL), or MDS/MPN not otherwise specified (NOS). A total of 101 patients were included (median age 71 years). MDS/MPN *SF3B1*-T showed a significant survival advantage compared with MDS/MPN NOS and aCML/CNL (OS $p=0.0058$, LFS $p=0.012$). aCML/CNL displayed the worst outcomes and most genetic complexity. Across the overall cohort, IPSS-M demonstrated the highest discriminative ability and calibration accuracy for both OS and LFS, outperforming CMML-directed models, including BLAST-clinical and BLAST-molecular whereas disease-specific scores provided optimal stratification within individual entities but failed to adequately predict outcomes in MDS/MPN NOS. In this real-world analysis, IPSS-M emerged as the most robust prognostic framework across MDS/MPN entities other than CMML. The inability of current tools to reliably stratify patients with MDS/MPN NOS underscores the biological heterogeneity of this category and highlights the urgent need for integrated clinical and genomic prognostic models.

https://doi.org/10.1007/s10238-026-02287-0

Published online: 01 September 2026

Springer

Introduction

Myelodysplastic/Myeloproliferative overlap syndromes (MDS/MPN) represent a heterogenous group of myeloid neoplasms characterized by overlapping dysplastic and proliferative features. In 2022, WHO 5th and ICC classifications updated and expanded MDS/MPN group, now including chronic myelomonocytic leukemia (CMML), MDS/MPN with neutrophilia or atypical chronic myeloid leukemia (aCML), MDS/MPN neoplasm with *SF3B1* mutation and thrombocytosis (MDS/MPN *SF3B1*-T) and MDS/MPN not otherwise specified (NOS), not meeting the criteria for a defined category [1, 2]. Although CMML features, including molecular underpinnings and outcomes, have been thoroughly investigated [3], biological and clinical characteristics of the other entities, mainly investigated in small and heterogeneous populations, are less defined. In particular, MDS/MPN *SF3B1*-T, defined by thrombocytosis and anemia, is characterized by frequent somatic hits in MPN canonical drivers (*JAK2*: 30–60%, *MPL*: 5%) with normal karyotype (90%), a low rate of progression to acute myeloid leukemia (AML, 5–10%) and long-term survival [4–9]. aCML, defined by leukocytosis ($\geq 13 \times 10^9$/L WBC), with circulating immature myeloid cells and cytopenia, is usually characterized by a high mutational burden and dismal prognosis [10–12]. Intriguingly, recent findings highlighted a remarkable clinical and biological overlap between aCML and chronic neutrophilic leukemia (CNL), suggesting that they represent a continuum of the same entity [13]. Finally, MDS/MPN NOS, defined by thrombocytosis and/or leukocytosis, mixed myeloproliferative and myelodysplastic features, not meeting criteria for any other MDS/MPN, MDS or MPN entity, present a highly heterogeneous biological profile and intermediate prognosis between the two previously described entities [5, 14, 15]. Most of these observations come from single-center or limited experiences thereby limiting their generalizability. Real-world studies are therefore essential to better define disease biology, treatment patterns, and long-term outcomes, as well as to evaluate the performance of existing prognostic models in unselected patient cohorts.

In this context, the present study aims to provide a comprehensive real-world analysis of MDS/MPN syndromes other than CMML, focusing on clinical characteristics, molecular features, survival outcomes, and the comparative performance of currently available prognostic scoring systems across different disease subtypes.

Methods

Patients

Adult patients (age > 18 years) fulfilling diagnosis of MDS/MPN syndromes other than CMML were retrospectively enrolled from 17 Italian centers. Due to the rarity of these diseases and their shared biological features, aCML and CNL patients were pooled together for the purpose of the analysis. Demographic and clinical information, including age, gender, complete blood count (CBC), bone marrow blasts, and karyotypic and genetic information were collected at diagnosis. Data on treatment and outcome were collected as well. In addition to characterizing the biological and clinical features of MDS/MPN entities, we applied MDS – and CMML-oriented risk scores, including IPSS-M [16] and BLAST [17] models, to the cohort. Furthermore, we applied disease-specific risk scores within individual entities, including *SF3B1*-score (clinical and molecular) [18] and AAA (triple A) model [19] for MDS/MPN *SF3B1*-T (given the common MPN-driver genes mutations) and Mayo [11] and aCML/CNL score [13] for aCML/CNL. The study was approved by the local ethics committees and was conducted in accordance with the Declaration of Helsinki.

Statistics

Quantitative variables were expressed as median and range. Qualitative variables were expressed as numbers and percentages. For all relevant comparisons, the Kruskal–Wallis test was used. Fisher's exact test or the chi-squared

test were used for testing independence between groups, where appropriate. Overall survival (OS) rate was calculated from the date of diagnosis to death by any cause or the last known follow-up visit for censored patients. Leukemia-free survival (LFS) rate was calculated from the date of diagnosis to evolution to leukemia, death by any cause or the last known follow-up visit for censored patients. Survival curves were estimated using the Kaplan–Meier method and compared with respect to the patients' demographic and clinical characteristics using the Log-Rank test. Concordance between prognostic systems was evaluated using Cohen's kappa coefficient; for comparative purposes, IPSS-M risk tiers were collapsed into three risk tiers to allow direct comparison with BLAST-clinical and BLAST-molecular models. Discriminative ability of the prognostic models was assessed using time-dependent receiver operating characteristic (ROC) curves and the area under the curve (AUC) for both OS and LFS. Model performance was further evaluated using Harrell's concordance index (c-index), calculated at 2 years. Calibration of the predicted risk of death at 2 years was assessed using bootstrap-corrected calibration plots, comparing predicted and observed risks across risk strata; mean absolute calibration error was calculated as a summary measure of calibration accuracy. All statistical tests were two-sided; a p-value ≤ 0.05 was considered statistically significant. All analyses and data visualization were generated using the following statistical programs: IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp., R version 4.4.0, Excel Microsoft Office 365 and GraphPad Prism (8.4.0).

Results

Overall population: clinical and molecular characteristics

A total of 101 patients were enrolled (M/F: 60/41, median age 71 years), including 32 MDS/MPN *SF3B1*-T, 25 aCML/CNL, and 44 MDS/MPN NOS. As expected, aCML/CNL showed higher WBC (34 vs 8 vs $11 \times 10^3/m^3$ in MDS/MPN *SF3B1*-T and MDS/MPN NOS, respectively; $p < 0.0001$), absolute neutrophil count (ANC, 25 vs 5 vs $7 \times 10^3/m^3$ in MDS/MPN *SF3B1*-T and MDS/MPN NOS; $p < 0.0001$), absolute lymphocyte count (ALC, 3.5 vs 2 vs $2 \times 10^3/m^3$ in MDS/MPN *SF3B1*-T and MDS/MPN NOS; $p = 0.0002$), and absolute monocyte count (AMC, 0.9 vs 0.4 vs $0.5 \times 10^3/m^3$ in MDS/MPN *SF3B1*-T and MDS/MPN NOS; $p = 0.0004$), whereas MDS/MPN SF3B1-T was characterized by higher platelet counts (605.5 vs 175 vs $261 \times 10^3/m^3$ in aCML/CNL and MDS/MPN NOS;$p < 0.0001$) and lower hemoglobin levels (9.1 vs 10.6 vs 11.2 g/dl in aCML/CNL and MDS/MPN NOS; $p = 0.001$). Furthermore, aCML/CNL presented the highest number of mutations (median 4 vs 3 and 2 in MDS/MPN *SF3B1*-T and MDS/MPN NOS, respectively; $p = 0.0006$. Supplementary Fig. 1). When analyzing treatment received, aCML/CNL patients received MDS-directed treatment, such as hypomethylating agents, more frequently as compared to other disease entities (24% vs 0% and 4.5% in MDS/MPN *SF3B1*-T and MDS/MPN NOS; $p = 0.0021$) and hematopoietic stem cell transplantation (8% vs 0% in both MDS/MPN *SF3B1*-T and MDS/MPN NOS; $p = 0.045$), while MDS/MPN *SF3B1*-T received more frequently erythropoiesis-stimulating agents (59% vs 12% vs 16% in aCML/CNL and MDS/MPN NOS; $p < 0.0001$) with no differences in terms of patients receiving 5-hydroxyurea (41% vs 44% vs 34% in MDS/MPN *SF3B1*-T, aCML/CNL and MDS/MPN NOS; p=ns). No significant differences were observed in age, sex distribution, karyotype abnormalities and bone marrow blasts across groups (Table 1). Karyotype information was available in 86 patients and NGS screening in 73. Most patients had normal karyotype (NK, 80%), while the most frequently detected cytogenetics abnormalities were trisomy(8) (6%) and del(5) (3.5%). The most common gene mutations involved *ASXL1* (49%), followed by *SF3B1* (31.5%), *SRSF2* (30%), *JAK2* (25%) and *TET2* (25%) (Fig. 1A). When investigating variant allele frequencies (VAF) of these mutations across different entities, we found no significant differences (Supplementary Fig. 2).

Table 1 Demographic, clinical and biological characteristics of the study cohort

		MDS/MPN (n=101)	MDS/MPN *SF3B1*-T (n=32)	aCML/CNL (n=25)	MDS/MPN NOS (n=44)	p
Age	Median (Range)	71 (45–90)	73 (57–90)	72 (57–82)	69 (45–88)	0.1816
Gender	M (%)	60 (59)	18 (56)	15 (60)	27 (61)	0.9022
WBC	$10^3/m^3$, median (range)	11.5 (1.9–113.6)	7.9 (1.9–14.6)	34 (13–113.7)	11.4 (2.5–58.2)	**<0.0001**
ANC	$10^3/m^3$, median (range)	7.6 (0.8–101.3)	4.7 (0.8–11.7)	25.3 (91–102.3)	7.4 (1.1–48.9)	**<0.0001**
AMC	$10^3/m^3$, median (range)	0.5 (0–5.4)	0.4 (0.07–0.9)	0.9 (0.04–5.4)	0.5 (0.05–2.2)	**0.0004**
ALC	$10^3/m^3$, median (range)	2.4 (0.4–8.1)	1.9 (0.4–4.3)	3.5 (1.5–8.1)	2.4 (0.4–6.6)	**0.0002**
Platelets	$10^3/m^3$, median (range)	409.5 (18–1507)	605.5 (459–1507)	175 (64–1008)	261 (18–1271)	**<0.0001**
Hb	g/dl, median (range)	9.8 (6.9–16)	9.1 (7.3–11.3)	10.6 (7–14.1)	11.2 (6.9–16)	**0.0010**
Bone marrow blasts≥5%	N (%)	8 (8)	1 (3.2)	4 (16)	3 (2.3)	0.1599
	NA	2	1	0	1	
Cytogenetics	Normal Karyotype (%)	67 (77.9)	24 (75)	17 (77.3)	26 (81.2)	0.8311
	NA	15	0	3	12	
Molecular screening	N of mutations, median (range)	3 (0–8)	3 (1–6)	4 (1–8)	2 (0–7)	**0.0006**
	NA	28	13	2	13	
Treatment	HMA, n (%)	8 (7.9)	0	6 (24)	2 (4.5)	**0.0021**
	5-HU, n (%)	39 (38.6)	13 (40.6)	11 (44)	15 (34.1)	0.6907
	ESA, n (%)	29 (28.7)	19 (59.4)	3 (12)	7 (15.8)	**<0.0001**
	HSCT, n (%)	2 (2)	0	2 (8)	0	**0.045**

5-HU: 5-hydroxyurea; aCML: atypical chronic myeloid leukemia; ALC: absolute lymphocyte count; AMC: absolute monocyte count; ANC: absolute neutrophils count; CNL: chronic neutrophilic leukemia; ESA: Erythropoietin stimulating agents; Hb: hemoglobin; HSCT: hematopoietic stem cell transplantation; M: male; MDS/MPN: myelodysplastic/myeloproliferative syndromes; N: number; NA: not available; NOS: not otherwise specified; WBC: white blood cell

Overall population – risk stratification and survival outcomes

At a median follow-up of 25.5 months, MDS/MPN *SF3B1*-T showed significantly better OS and LFS compared with MDS/MPN NOS and aCML/CNL, which displayed the worst outcomes, both in terms of OS and LFS (median OS and LFS of 157 months in MDS/MPN *SF3B1*-T vs 78 and 39 months in MDS/MPN NOS and aCML/CNL, respectively; OS p=0.0058, LFS p=0.012; Fig. 1B and supplementary Fig. 3).

When applying different risk stratification models, IPSS-M classified a higher proportion of patients into lower-risk categories, whereas most patients were assigned to intermediate- or high-risk tiers by BLAST-based scores (Fig. 1C). Although BLAST-clinical and BLAST-molecular showed good mutual concordance (κ=0.773), their agreement with IPSS-M was limited (Fig. 1C).

IPSS-M stratification correctly stratified patients according to risk tiers (OS: p=0.073, Fig. 1D. LFS: p=0.064, supplementary Fig. 4A), as well as BLAST-clinical (OS: p=0.009, Fig. 1E. LFS: p=0.0056, supplementary Fig. 4B). On the other hand, BLAST-molecular stratification was less effective, showing a prognostic overlap between intermediate and high-risk tiers (OS: p=0.35, Fig. 1F; LFS: p=0.28, supplementary Fig. 4C). ROC curves analysis showed the highest AUC for IPSS-M, followed by BLAST-clinical and BLAST-molecular (0.798 vs 0.761 vs 0.69 for OS and 0.809 vs 0.771 vs 0.712 for LFS, respectively; Fig. 1G and supplementary Fig. 5). 2-year c-index confirmed the higher efficiency of IPSS-M stratification over BLAST-clinical and molecular both in terms of LFS (0.765 vs 0.674 vs 0.672, respectively; supplementary Fig. 6A) and OS (0.753 vs 0.668 vs 0.669, respectively; supplementary Fig. 6A). In the same line, calibration analysis showed close agreement between predicted and observed probabilities in IPSS-M for both OS (mean error: 0.044) and LFS (mean error: 0.022), with poorer calibration and bidirectional error for BLAST-clinical and BLAST-molecular (Supplementary Fig. 7 and 8). Among the 43 high-risk patients, according to BLAST-clinical, 15 were younger than 70 years, including 5 MDS/MPN-*SF3B1*-T, 5 aCML/CNL and 5 MDS/MPN NOS. HSCT was performed in two patients (both aCML/CNL).

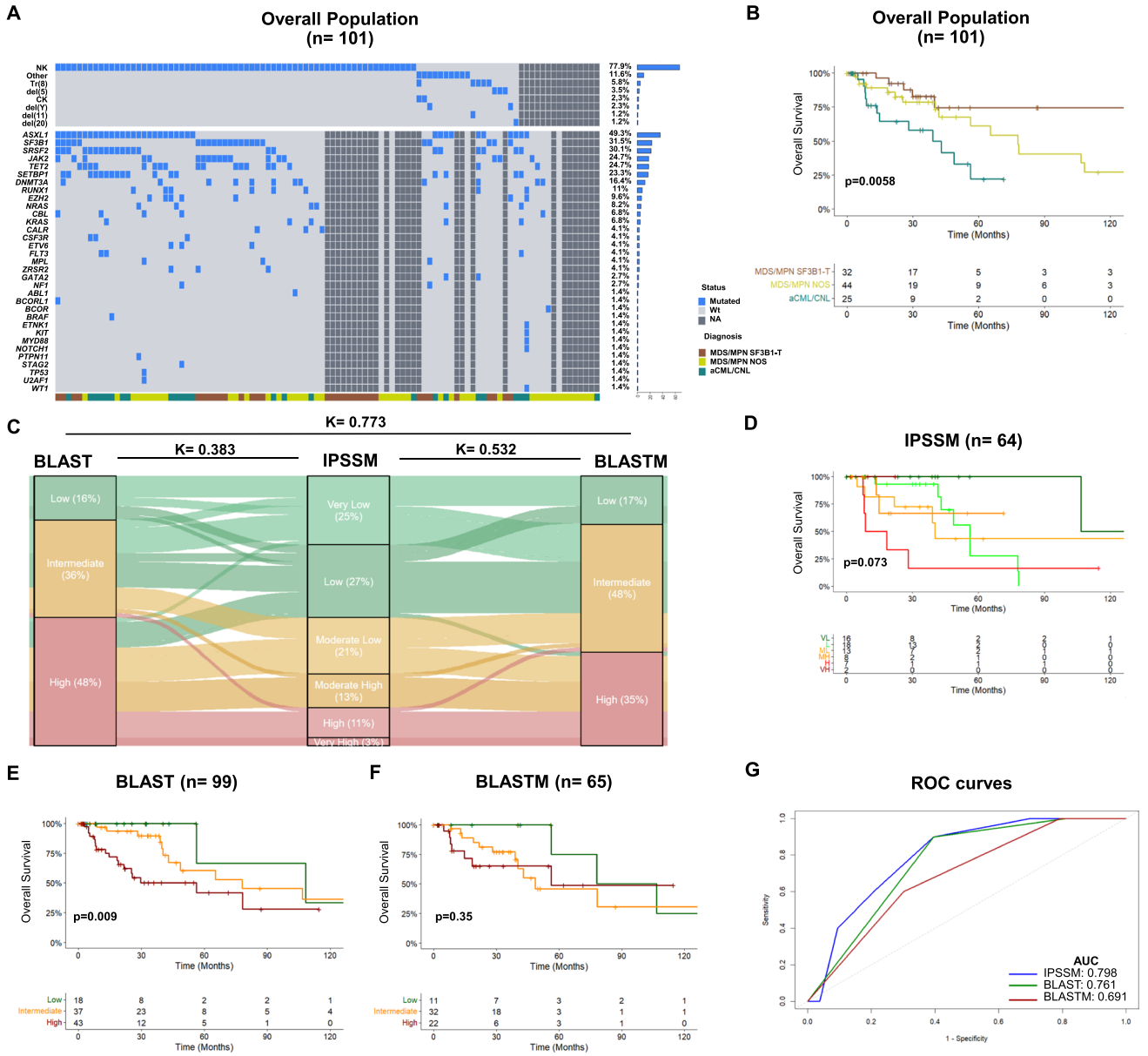

Fig. 1 Clinical features, molecular characteristics and outcomes of the whole MDS/MPN cohort. (**A**) Oncoplot. Colorimetric scales representing mutational status and diagnosis are shown in the figure. The oncoplot shows only the mutations detected at t-NGS screening. (**B**) Survival analysis among different nosologic entities. (**C**) Sankey plot. The diagram shows the risk tiers shifting among BLAST-clinical, IPSS-M and BLAST-molecular scores. Concordance indexes are reported above the tools' labels. (**D-F**) Survival curves according to IPSS-M, BLAST-clinical and BLAST-molecular stratifications. (**G**) ROC curves for risk models. aCML/CNL: atypical chronic myeloid leukemia/chronic neutrophilic leukemia; AUC: area under the curve; BLAST: BLAST-clinical; BLASTM: BLAST-molecular; CK: complex karyotype; H: high; L: low; MDS/MPN: Myelodysplastic/Myeloproliferative overlap syndromes; MH: moderate high; ML: moderate low; NA: not available; NGS: targeted next-generation sequencing; NK: normal karyotype; NOS: not otherwise specified; ROC: receiver operator curve; VH: very high; VL: very low

MDS/MPN *SF3B1*-T

32 MDS/MPN SF3B1-T cases were included. Most of them presented normal karyotype (75%), with the most frequently-detected karyotype abnormalities including complex karyotype, trisomy(8), del(5), del(Y), observed in 2 patients each (6.2%). Apart from *SF3B1* mutation, detected in all cases, the most frequently-detected genetic lesions affected *JAK2, ASXL1, DNMT3A* and *TET2* genes (47%, 26%, 21% and 21%, respectively; Fig. 2A). When analyzing outcomes, the best stratification was offered by BLAST-clinical score (OS: p = 0.065, LFS: p = 0.03) which outperformed not only IPSS-M and BLAST-molecular, but also specific and MPN-oriented stratification tools (AAA) (Fig. 2B-G, supplementary Fig. 9A-E). When investigating the impact of the most frequent gene mutations on outcomes, we observed a dismal prognosis carried by *ASXL1* mutations when compared to wt counterparts (OS: p = 0.031; LFS: p = 0.17; supplementary Fig. 10).

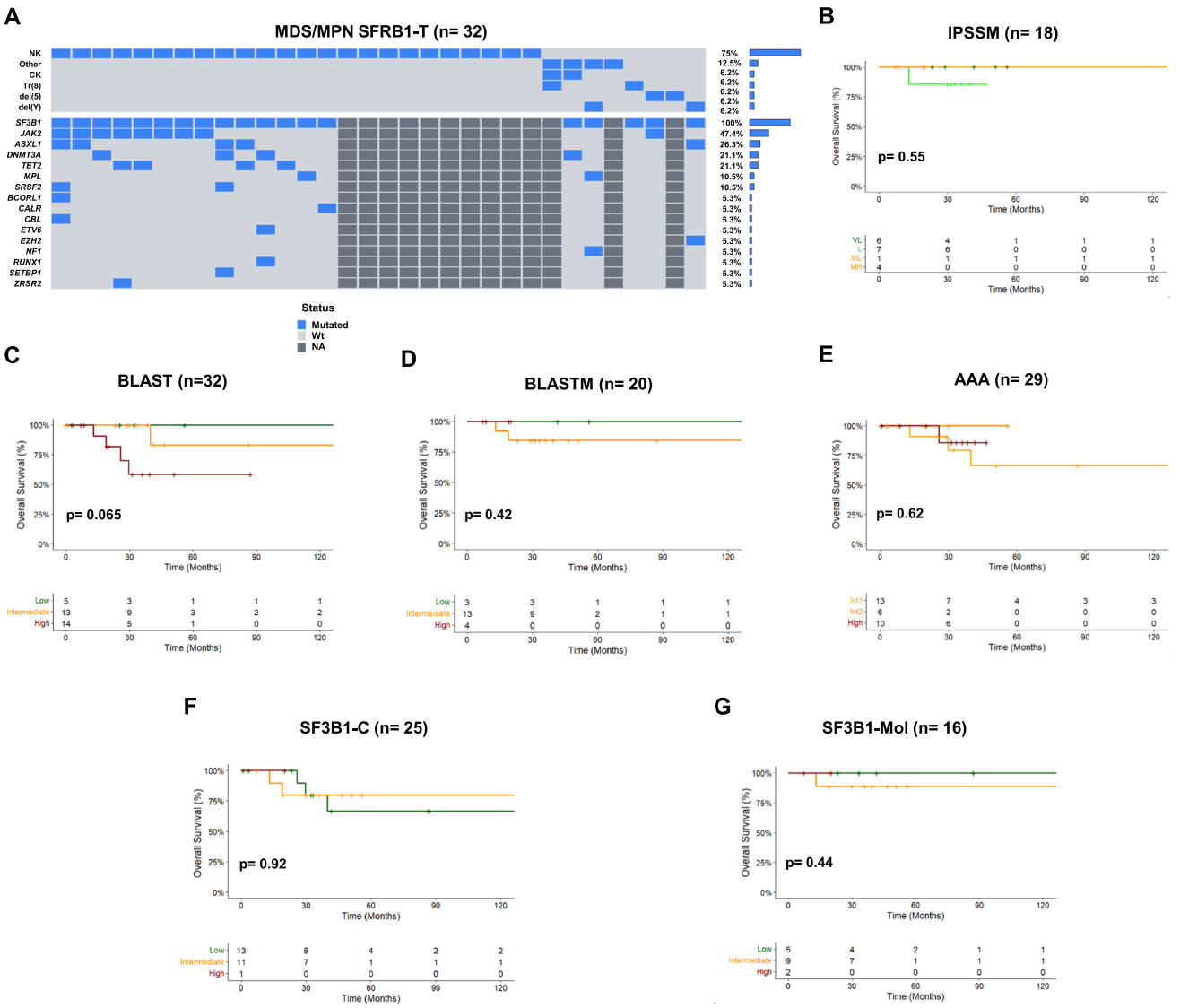

Fig. 2 MDS/MPN SF3B1-T analysis. (**A**) Oncoplot. Colorimetric scale representing mutational status is shown in the figure. (**B-G**) Survival curves according to IPSS-M, BLAST-clinical, BLAST-molecular, AAA, *SF3B1*-clinical, *SF3B1*-molecular stratifications. BLAST: BLAST-clinical; BLASTM: BLAST-molecular; CK: complex karyotype; L: low; MDS/MPN: Myelodysplastic/Myeloproliferative overlap syndromes; MH: moderate high; ML: moderate low; NA: not available; NK: normal karyotype; *SF3B1*-C: *SF3B1*-clinical score; *SF3B1*-M: *SF3B1*-molecular score; VL: very low

aCML/CNL

Among the 25 patients with aCML/CNL, 77.3% presented normal karyotype. Trisomy(8) was the most frequently detected karyotype aberrancy (9%), followed by del(20) (4.5%). NGS screening showed high rates of mutations in *ASXL1*, *SETBP1* and *SRSF2* genes (87%, 61% and 61%, respectively) (Fig. 3A). Among the risk tools, the best performance was provided by CNL/aCML score both in terms of OS (p = 0.00032) and LFS (p = 0.0002) (Supplementary Fig. 11). No notable differences in patient outcomes were found when we grouped them based on the most frequently identified genetic mutations (Supplementary Fig. 12). In the aCML/CNL cohort, 9 were younger than 70 years. Of these, 2 underwent allogeneic HSCT: one patient is alive after 4 months of follow-up, whereas the other died from transplant-related complications. Among the remaining 7 patients younger than

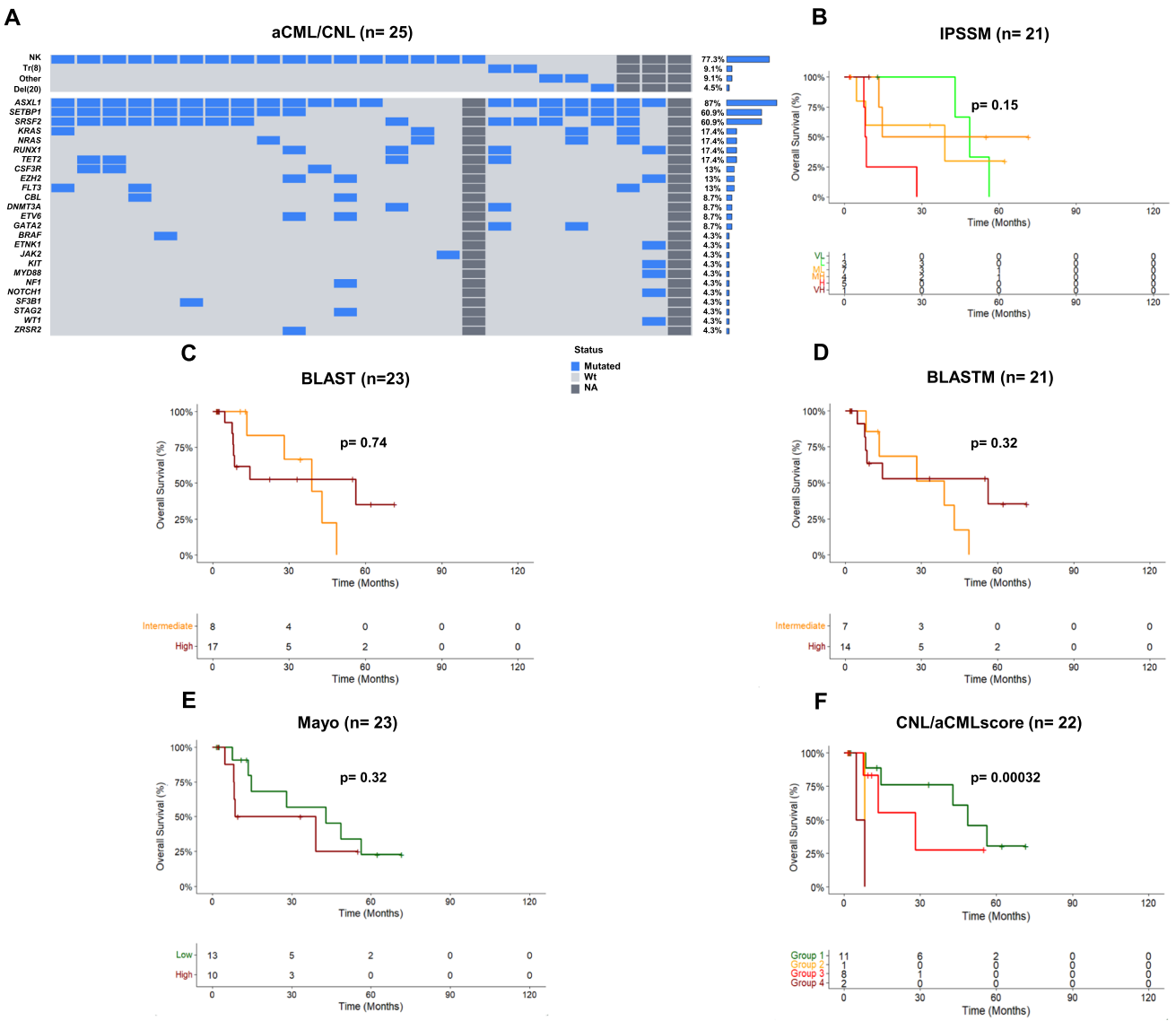

Fig. 3 aCML/CNL analysis. (**A**) Oncoplot. Colorimetric scale representing mutational status is shown in the figure. (**B-F**) Survival curves according to IPSS-M, BLAST-clinical, BLAST-molecular, Mayo score, aCML/CNL score stratifications. aCML/CNL: atypical chronic myeloid leukemia/chronic neutrophilic leukemia; BLAST: BLAST-clinical; BLASTM: BLAST-molecular; H: high; L: low; MH: moderate high; ML: moderate low; NA: not available; NK: normal karyotype; VH: very high; VL: very low

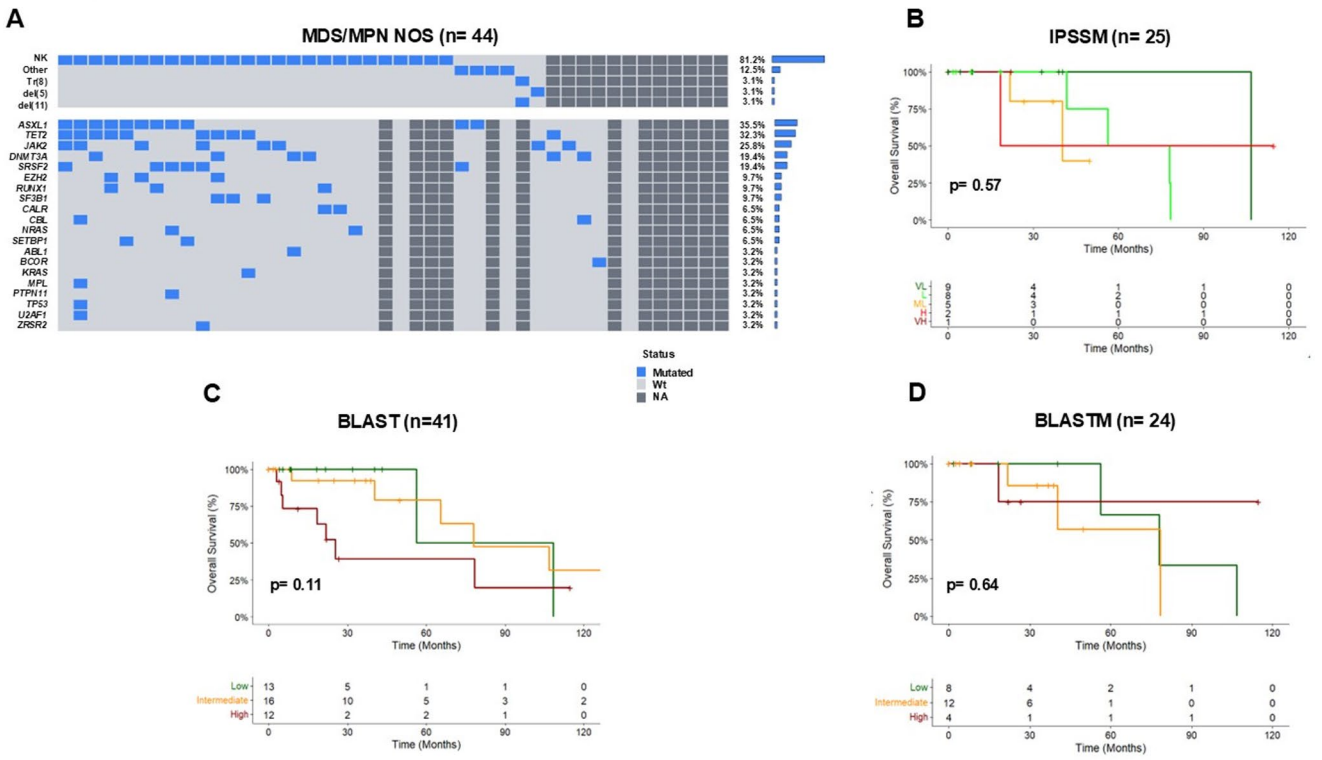

Fig. 4 MDS/MPN NOS analysis. (**A**) Oncoplot. Colorimetric scale representing mutational status is shown in the figure. (**B-D**) Survival curves according to IPSS-M, BLAST-clinical, BLAST-molecular. BLAST: BLAST-clinical; BLASTM: BLAST-molecular; H: high; L: low; MDS/MPN: Myelodysplastic/Myeloproliferative overlap syndromes; ML: moderate low; NA: not available; NK: normal karyotype; NOS: not otherwise specified; VH: very high; VL: very low

70 years, 2 had significant comorbidities that precluded HSCT. Two additional patients experienced rapid progression to AML before transplantation could be considered; one died shortly thereafter, whereas the other died after receiving a few cycles of azacitidine plus venetoclax. The remaining 3 patients (two aged 64 years and one aged 69 years) were all classified as low risk according to the Mayo score, whereas according to the aCML/CNL score, two belonged to risk group 1 and one to risk group 3. The latter patient received azacitidine for 20 months before progressing to AML and subsequently died shortly after treatment with azacitidine plus venetoclax.

MDS/MPN NOS

Finally, we analyzed MDS/MPN NOS (n = 44). Normal karyotype was present in 81% of cases, followed by trisomy(8), del(5) and del(11) (1 patient each, 3%). The most frequent gene mutations included *ASXL1* (35.5%), *TET2* (32%) and *JAK2* (26%). Of note, neither IPSS-M/BLAST risk scores and single gene mutations were able to predict outcomes in this specific subset of patients (Fig. 4**,** supplementary Fig. 13–14).

Discussion

In this study, we provide a comprehensive clinical, cytogenetic, molecular and long-term outcome analysis of a cohort of MDS/MPN patients in a real-world setting. Consistent with previous reports[5], we observed marked phenotypic differences across nosologic entities. In particular, aCML/CNL patients exhibited a more proliferative

profile, characterized by remarkable leukocytosis and inferior outcomes, whereas in MDS/MPN *SF3B1*-T patients prevailed anemia and thrombocytosis with better prognosis. MDS/MPN NOS presented intermediate features between the previous two entities, both in terms of clinical parameters and prognosis. Interestingly, molecular screening was available in most aCML/CNL patients (92%), whereas it was not available in 30–40% of MDS/MPN *SF3B1*-T and MDS/MPN NOS cases. This finding likely reflects both a still incomplete nationwide implementation of routine NGS testing in a high-income country such as Italy (possibly reflecting regional differences) and the greater diagnostic complexity of aCML/CNL, which may prompt a more extensive molecular investigation and whose diagnostic delay may contribute to its poorer prognosis. In this line, broader implementation of molecular profiling together with the refinement of prognostic models in higher-risk MDS/MPN entities, such as aCML/CNL and MDS/MPN NOS, may better inform therapeutic decision-making, including timely referral for allogeneic HSCT evaluation. Although HSCT is associated with substantial treatment-related morbidity and mortality, previous reports showed its efficacy and feasibility, with 5-year relapse-free survival rates of up to 36% in aCML [20] and 3-year overall survival approaching 50% in MDS/MPN NOS [21]. Accordingly, recent recommendations from European Bone Marrow Transplantation suggest considering HSCT in all aCML/CNL patients and in high-risk MDS&MPN-SF3B1-T and MDS/MPN NOS patients [22].

From a genetic standpoint, we observed a normal karyotype in most of the patients, both in the overall population and, separately, in each disease spectrum. This result indeed highlights the importance of a deeper molecular analysis to further characterize these diseases and establish clonality in difficult-to-diagnose cases, considering the presence of at least one molecular driver in 94.5% of the overall population.

When analyzing different prognostic tools to assess risk in the pooled subtypes of myeloid neoplasia, we observed that IPSS-M had the highest predictive power compared with BLAST-clinical and -molecular. Beyond differences in discrimination, the limited concordance between prognostic models highlights substantial risk reclassification across systems. Sankey analyses revealed a systematic shift of patients classified as intermediate/high risk by BLAST-based scores into lower risk tiers when reassessed by IPSS-M. To further substantiate these findings, we analyzed calibration plots which suggested bidirectional miscalibration for both BLAST-clinical and BLAST-molecular across OS and LFS, characterized by underestimation of risk in lower-risk patients and overestimation in higher-risk patients. In contrast, IPSS-M showed closer agreement between predicted and observed outcomes across the spectrum, supporting more reliable absolute risk estimation. This finding may reflect the higher molecular granularity with subsequent broader applicability of IPSS-M and to a more specific disease-orientation of BLAST models. Nonetheless, all three tools showed acceptable risk prognostication (c-indexes above 0.65 in all the models for OS and LFS), with BLAST-clinical presenting the not-negligible advantage not to require cytogenetics and molecular data to be interrogated and thus being broadly available in virtually all the patients (in our case series 99 vs 64 and 65 in IPSS-M and BLAST-molecular, respectively).

When analyzing specific disease subtypes, we included in our investigation both disease-specific models and specific gene mutations. As a result, we observed the most robust predictors were higher BLAST-clinical score and *ASXL1* mutation in MDS/MPN *SF3B1*-T and higher aCML/CNL score in aCML/CNL. In MDS/MPN NOS, unfortunately, no risk stratification model or molecular marker was able to predict survival. This finding highlights the clinical and genetic heterogeneity of MDS/MPN NOS with subsequent inability of current models to adequately capture risk prognostication.

Several limitations of the present study should be acknowledged. First, the retrospective nature and limited sample of the overall population and of specific subgroups may have reduced the statistical power of certain analyses. Second, cytogenetic and molecular data were not available for all patients, reflecting variability in real-world diagnostic practices, preventing us from drawing definitive conclusions.

Nonetheless, our analysis provides a realistic representation of outcomes across MDS/MPN entities other than CMML. Our results support the preferential use of disease-adapted prognostic models for specific entities, while highlighting their limitations in unclassifiable categories. In particular, these findings underscore the need for integrated clinical and genomic approaches in MDS/MPN NOS, representing a biologically heterogeneous category in which improved clinical and genomic risk models are needed.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10238-026-02287-0.

Acknowledgements L.G. wish to thank AMICI DI BEAT LEUKEMIA Dr. Alessandro Cevenini Onlus and AIRC Fellowships for Italy Post-Doc 2025.

Author contributions L.G. data curation and analysis and wrote the manuscript. G.G.L., M.B., M.M., B.F., M.R., A.D.V., M.S., G.I., A.L.B., S.L.C., C.T., R.L., P.G., S.M., A.L.P., E.S., C.A., L.R., P.S., G.A., F.I., A.M., N.P., F.M., F.C., A.A., A.S., K.P., P.G., A.M.V., E.F., M.T.V., A.V. collected data and edited the manuscript. L.M. contributed with conceptualization, data analysis, editing and wrote the manuscript.

Funding L.G. received funding by thank AMICI DI BEAT LEUKEMIA Dr. Alessandro Cevenini Onlus and Italy Post-Doc AIRC fellowship.

Data availability The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics statement The review of medical records was approved by the internal Institutional Review Boards involved in this study in agreement with the Declaration of Helsinki.

Conflict of interest The authors declare no competing interests.

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