FONDAZIONE ITALIANA SINDROMI MIELODISPLASTICHE

Convegno della Fondazione Italiana Sindromi Mielodisplastiche

30 giugno 2025

Nuovi parametri molecolari per la diagnosi: la stratificazione prognostica dei pazienti con CMML

Dott.ssa Alessia Campagna

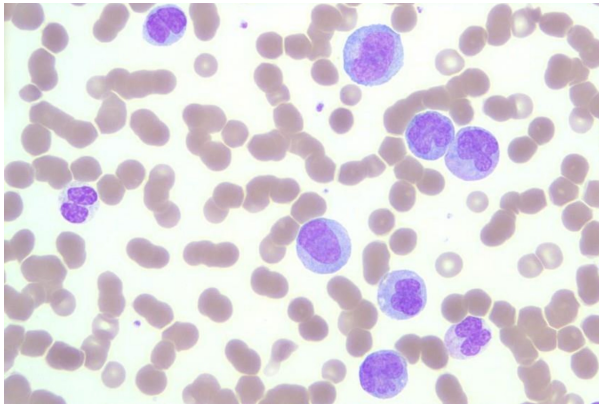
Humanitas Research Hospital

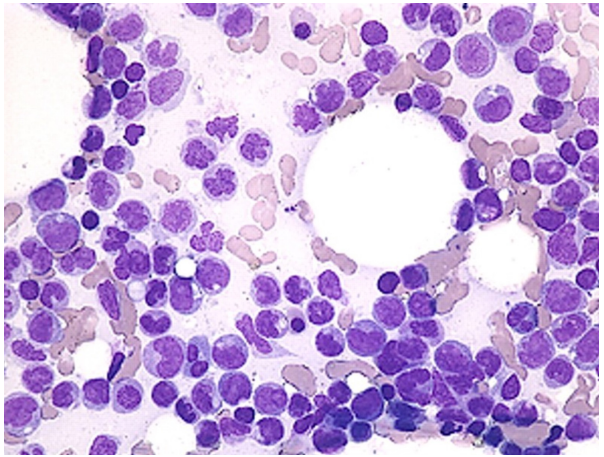
Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other

Chronic myelomonocytic leukemia (CMML) is a clonal hematopoietic stem and progenitor cell disorder characterized by the presence of:

- sustained (>3 months) peripheral blood (PB) monocytosis (≥0.5 x 10^9/L; monocytes ≥10% of white blood cell count)
- bone marrow dysplasia
- risk to transform to AML: 15%–20% over 3–5 y





Patnaik, Am J Hematol. 2024;99:1142–1165.

ICC 2022 and WHO 2022 criteria for diagnosis of CMML

Variable	ICC	5th edition of the WHO Classification
Absolute monocyte count	AMC ≥ 0.5 × 10^9/L, with monocytes being ≥10% of the WBC differential	[b]AMC ≥0.5 × 10^9/L, with monocytes being ≥10% of the WBC differential
Cytopenias	MDS-defining cytopenias	Not specified
Clonality	Abnormal karyotype, or myeloid driver mutations with a variant allele fraction ≥10% Without a clonal marker the AMC ≥ 1.0 × 10^9/L, along with ≥5% BM blasts, or BM dysplasia, or an abnormal immunophenotype	[c]Abnormal karyotype and/or presence of a myeloid driver mutation
CMML categorization	[a]CMML-1: <5% PB blasts and <10% BM blasts CMML-2: 5%–19% PB blasts and 10%–19% BM blasts, or the presence of Auer rods WBC < 13 × 10^9/L-MD-CMML WBC ≥ 13 × 10^9/L-MP-CMML	[a]CMML-1: <5% PB blasts and <10% BM blasts CMML-2: 5%–19% PB blasts and 10%–19% BM blasts, or the presence of Auer rods WBC < 13 × 10^9/L-MD-CMML WBC≥13 × 10^9/L-MP-CMML
Bone marrow aspirate and biopsy	Hypercellular marrows with increased BM monocytosis. No features of AML or MPN <20% blasts	[c]Dysplasia present in ≥1 cell lineage [b] < 20% blasts
Monocyte repartition-based flow cytometry	Not included	[c]Presence of classical monocytes (M01) >94%
Exclusionary criteria	*BCR::ABL1* Myeloid/lymphoid neoplasms with tyrosine kinase fusions	[b]*BCR::ABL1* MPN Myeloid/lymphoid neoplasms with tyrosine kinase fusions

Patnaik, Am J Hematol. 2024;99:1142–1165.

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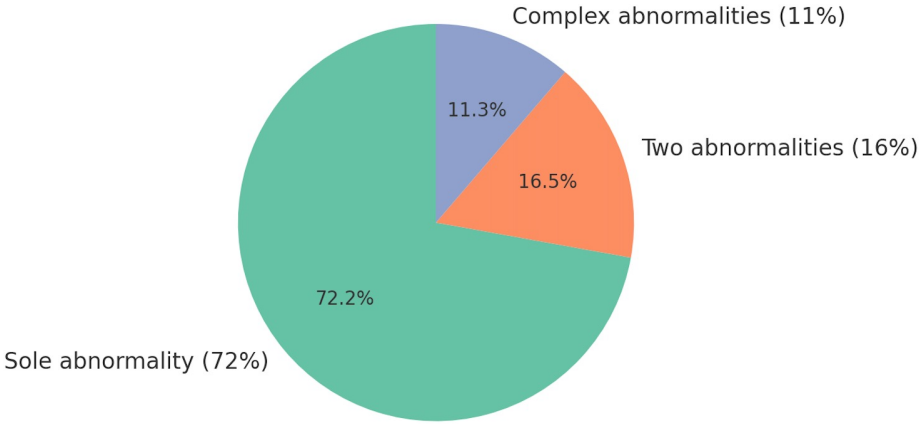
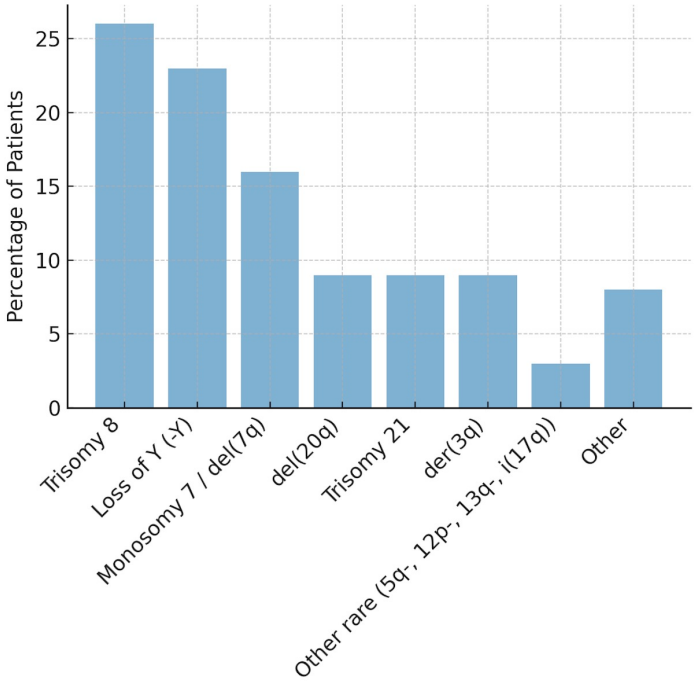
Patnaik, Am J Hematol. 2024;99:1142–1165.

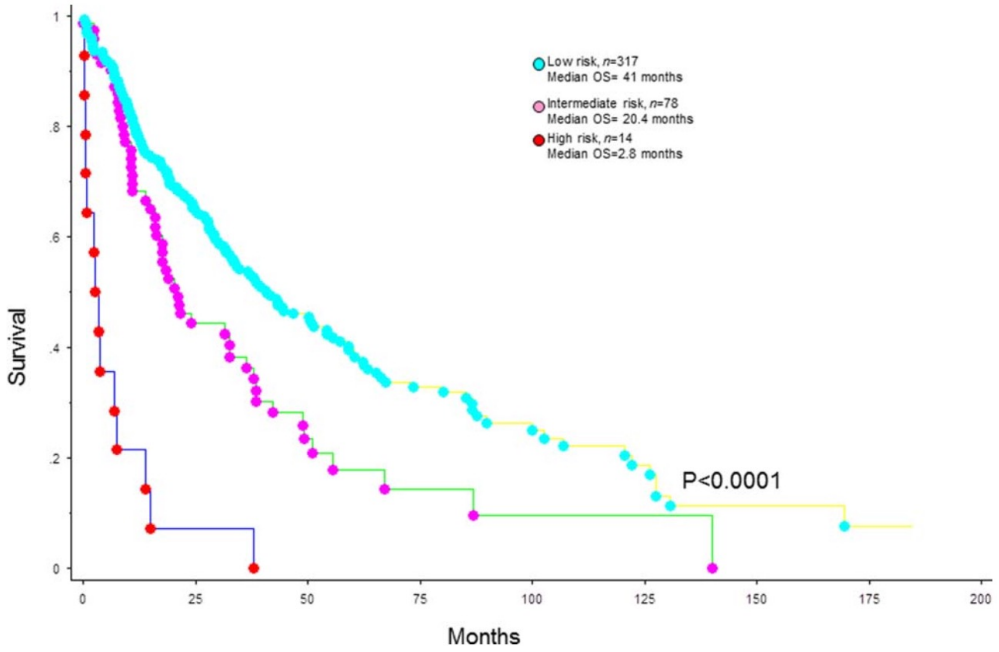
Clonal cytogenetic abnormalities are seen in ~30% of CMML





Adaptetd from Wassie et al., Am. J. Hematol. 89:1111–1115, 2014

CMML-specific cytogenetic risk classification



Low risk: normal karyotype, loss of Y chromosome, Isolated 3q rearrangements

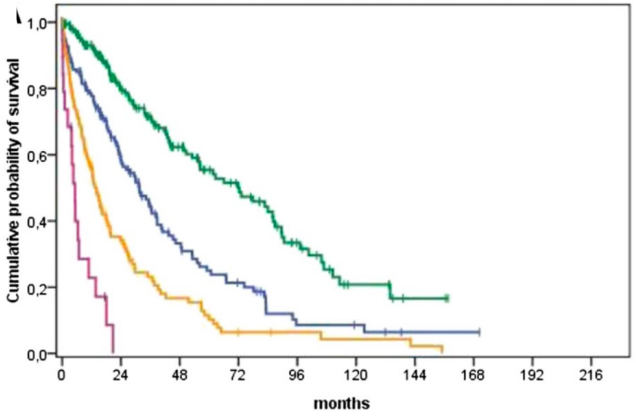
Intermediate risk: all other abnormalities (e.g., +8, –7/7q–, del(20q), +21, etc.)

High risk: Complex karyotype, Monosomal karyotype

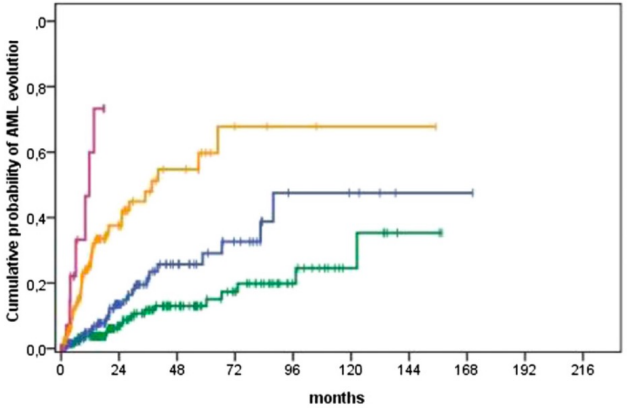
Wassie et al., Am. J. Hematol. 89:1111–1115, 2014

CMML-specific prognostic scoring system (CPSS)

Overall Survival



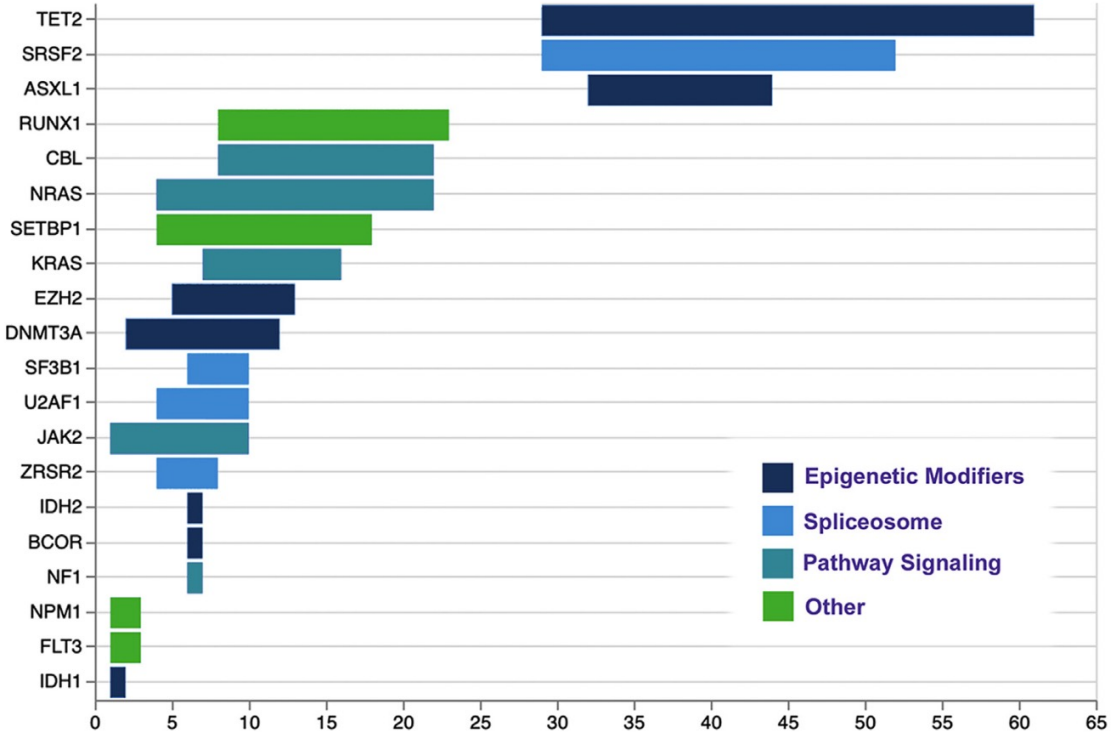
Risk of AML transformation



	Variable scores		
Variable	**0**	**1**	**2**
WHO subtype	CMML-1 blasts (including promonocytes) <5% in the PB and <10% in the BM	CMML-2 blasts (including promonocytes) from 5% to 19% in the PB and from 10% to 19% in the BM, or when Auer rods are present irrespective of blast count	—
FAB subtype	CMML-MD (WBC count $<13 \times 10^9$/L)	CMML-MP (WBC count $\geq 13 \times 10^9$/L)	—
CMML-specific cytogenetic risk classification*	Low	Intermediate	High
RBC transfusion dependency†	No	Yes	—

Such E et al. Blood. 2013 Apr 11;121(15):3005-15.

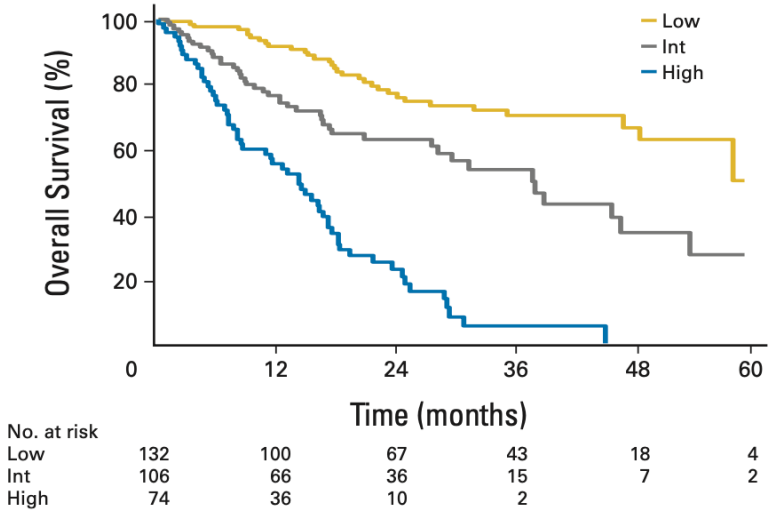
Relative frequencies of somatic mutations in patients with CMML



Curr Oncol Rep (2019) 21: 101 Best Practice & Research Clinical Haematology 33 (2020) 101131

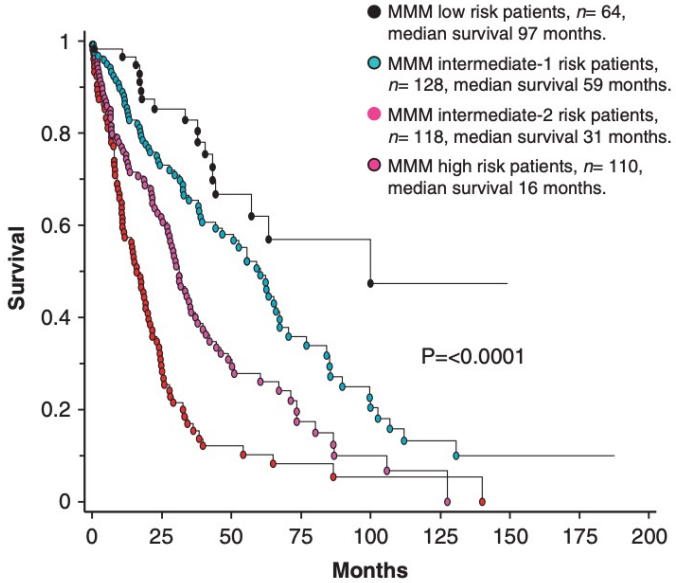
GFM score

1. Age >65 years
2. WBC >15 × 10^9/L
3. Anemia
4. Platelets <100 × 10^9/L
5. *ASXL1* mutation



Mayo Molecular Model

1. Increased absolute monocyte count >10 × 10^9/L
2. Presence of circulating blasts
3. Hemoglobin <10 g/dL
4. Platelet count <100 × 10^9/L
5. Frameshift and nonsense *ASXL1* mutations

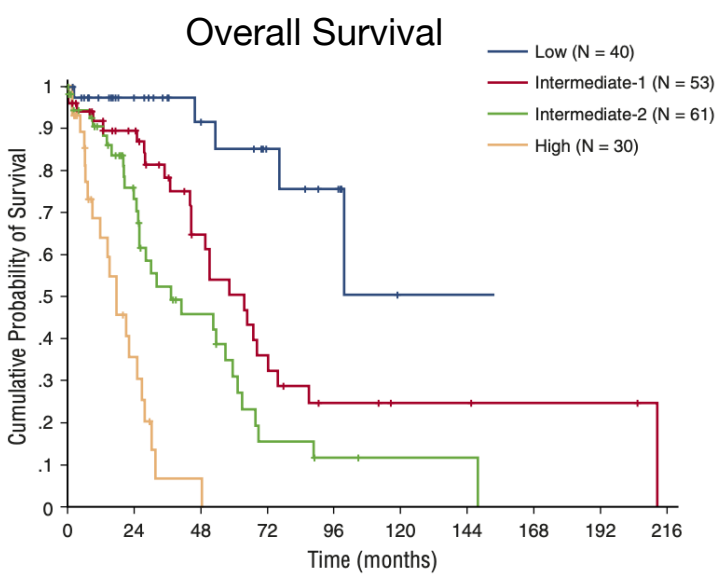


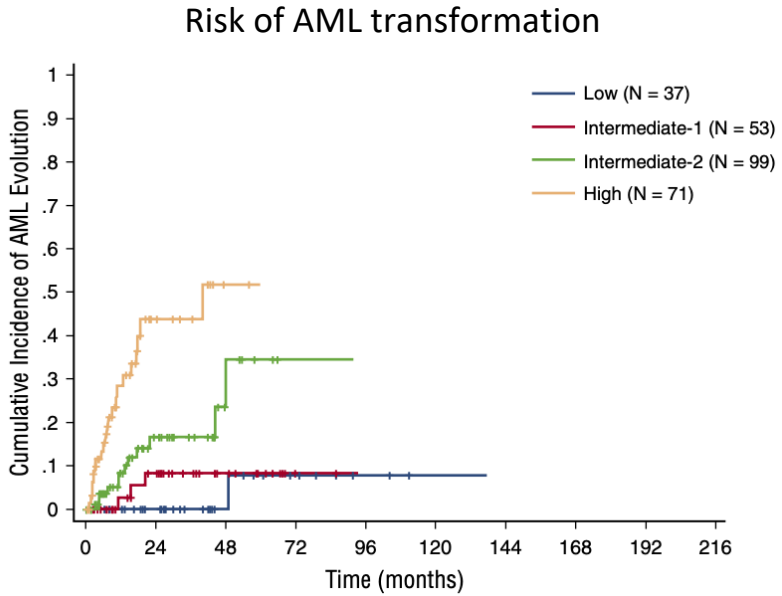
ASXL1 was the only mutation independently associated with adverse prognosis

Itzykson R et al. J Clin Oncol 2013
Patnaik et al., Leukemia 2013

1.Genetic risk groups as defined by CPSS cytogenetic risk stratification and gene mutations involving ASXL1, NRAS, SETBP1 and RUNX1.
2.Bone marrow blasts ≥5%.
3.WBC count ≥13 × 10?/L
4.Red blood cell transfusion dependancy

CPSS-mol



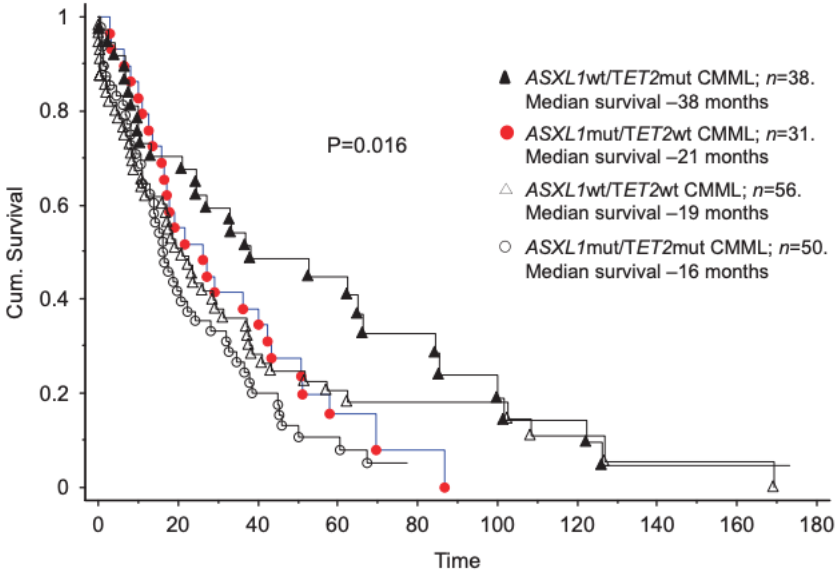


Mutations involving ASXL1, NRAS, SETBP1 and RUNX1

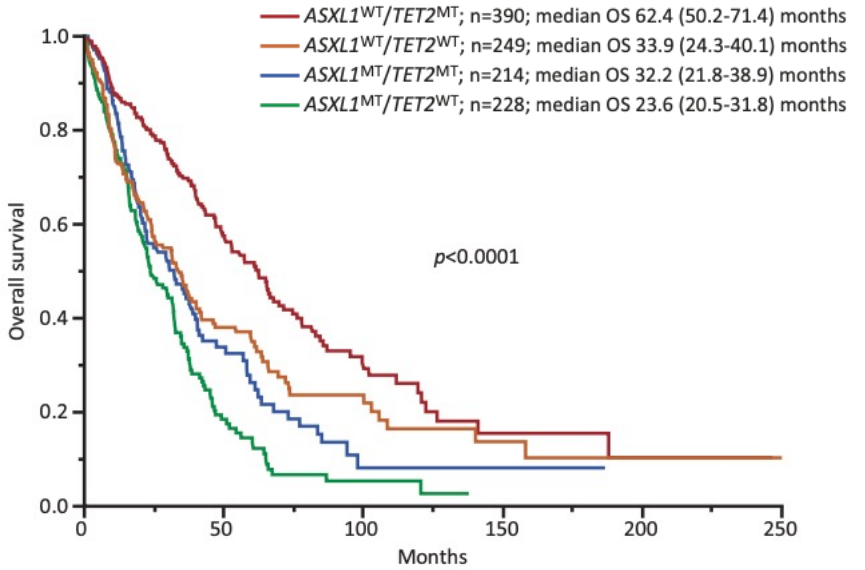
Elena C et al. Blood. 2016 Sep 8;128(10):1408-17

Prognostic impact of somatic mutations depends on co-mutational status

TET2 mutations confer favorable prognosis only in the absence of ASXL1

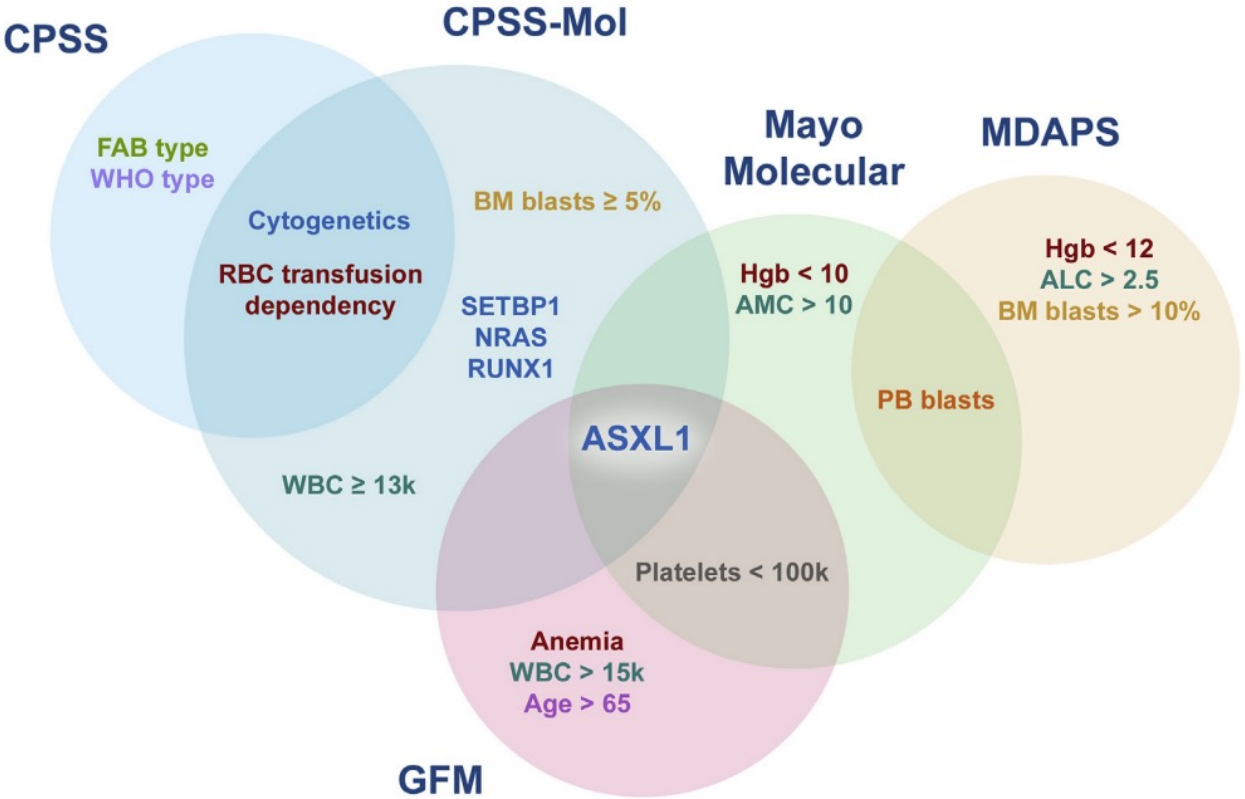


Patnaik MM et al. Blood Cancer J. 2016;6:e385.



Coltro G et al. Leukemia. 2020 May;34(5):1407-1421.

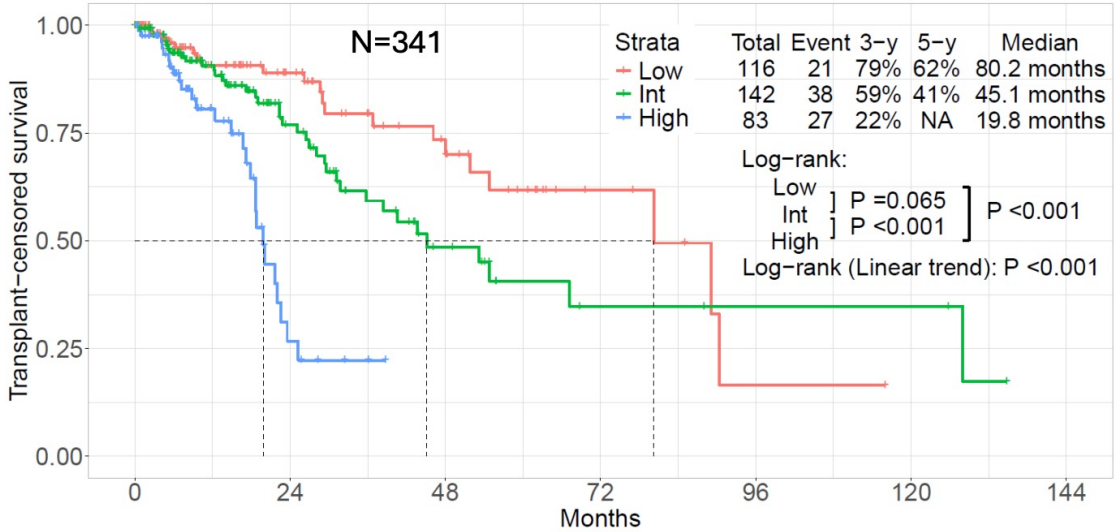
Overview of Prognostic Models in CMML



Best Practice & Research Clinical Haematology 33 (2020) 101131

BLAST and BLAST-mol score

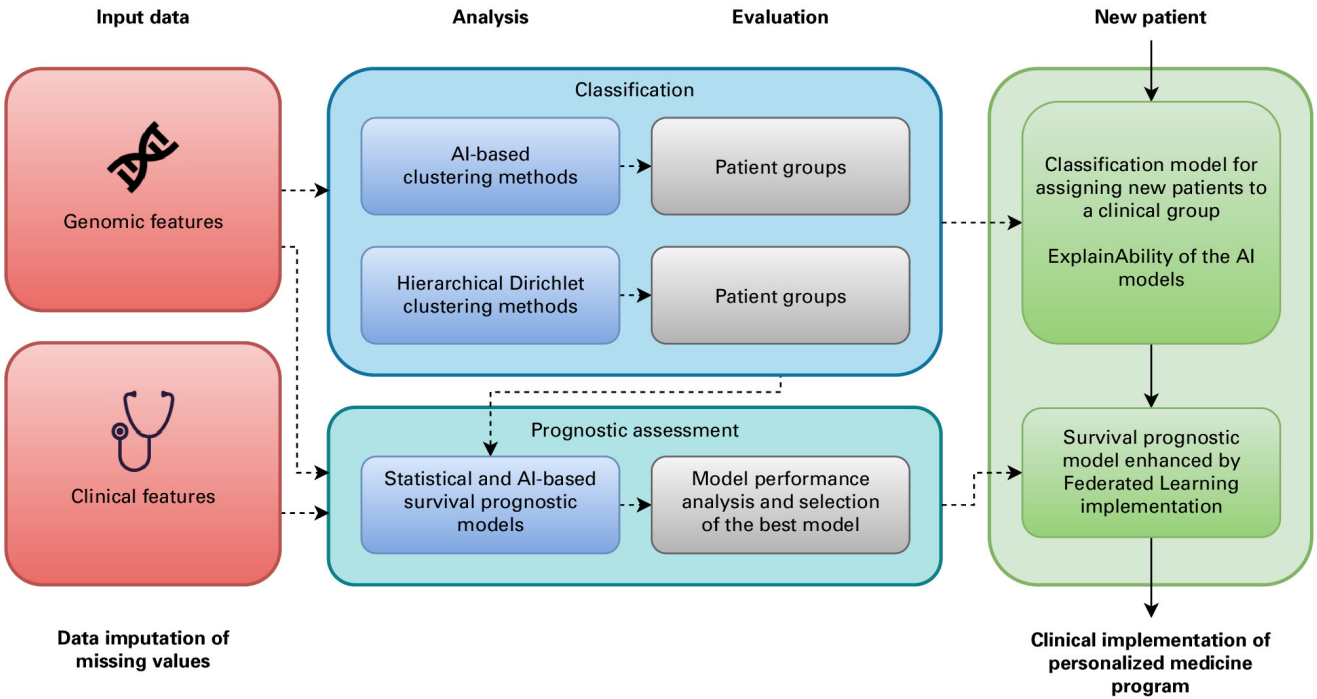
Circulating blasts ≥ 2%
Leukocytes ≥13 x 10^9/L
Anemia



Favorable genetic risk factors: TET2^{MUT}; PHF6^{MUT} wo unfavorable mutations
Unfavorable genetic risk factors: DNMT3A^{MUT}; U2AF1^{MUT}; BCOR^{MUT}; SETBP1^{MUT}; PTPN11^{MUT}; NRASMUT; RUNX1^{MUT}; TP53^{MUT}; ASXL1^{MUT}; and adverse karyotype defined by cytogenetic abnormalities (-Y or +8)
Intermediate genetic risk factors: all other

Tefferi A et al. Blood. 2025

An innovative framework for multi-modal analysis, classification and personalized prognostic assessment in hematology

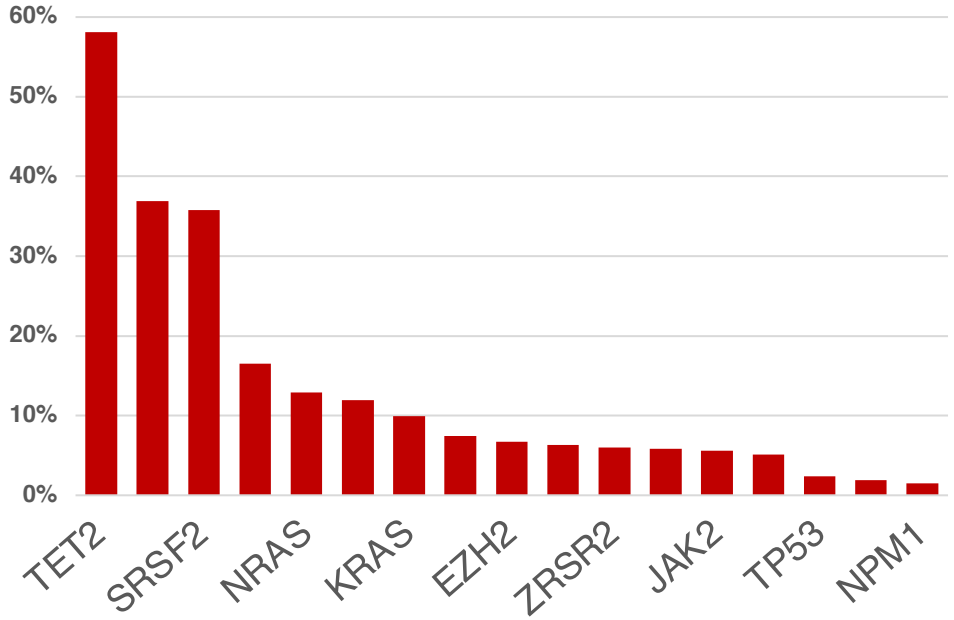


D'Amico et al., JCO-CCI 2024, PMID 38875514

Retrospective Study Population (N = 3,565)

WHO 2016 Classification	
CMML-0	1,470 (41.2)
CMML-1	1,138 (31.9)
CMML-2	620 (17.4)
Oligo-CMML	337 (9.5)
WHO 2022 Classification	
CMML-1	2,905 (81.5)
CMML-2	660 (18.5)
Age	70.8 (63-77)
Sex	
Female	1,153 (32.3)
Male	2,412 (67.7)
Laboratory Parameters	
White Blood Cells	9.2 (5.4-18.3)
Neutrophils	4.5 (2.2-9.6)
Monocytes	1.9 (1.2-3.9)
Hemoglobin	11.0 (9.2-12.7)
Platelets	112 (62-196)
Marrow Blasts	4 (2-8)
Allogeneic HSCT	769 (21.6)

- Cytogenetic and mutational information were collected locally
- P/LP variants (VAF >2%) were included in the analysis



Lanino L, Blood 144 (2024) 1003–1008

Mutation-Based Clustering Enhances Prognostic Stratification

Subgroup	Cluster-defining abnormalities	Assigned patients	Median OS, years (95% C.I.)	Median LFS, years (95% C.I.)
Splicing machinery	*SRSF2 + TET2*	7.9%	4.5 (3.4-7.5)	4.5 (3.3-7.5)
	ZRSR2 + TET2	3.1%	8.2 (4.3- NR)	8.0 (4.1-NR)
Splicing and additional higher-risk mutations	*SRSF2 + TET2 + ASXL1/RUNX1*	22.2%	3.2 (2.8-3.5)	2.4 (2.1-3.0)
	ZRSR2 + TET2 + EZH2/ASXL1	8.9%	1.9 (1.7-2.5)	1.6 (1.1-2.3)
Isolated SF3B1	*SF3B1*	6.6%	4.2 (3.7-4.8)	3.3 (2.9-4.1)
Signal transduction and tyrosine-kinase pathways	*CBL*	7.1%	3.9 (2.6-5.6)	3.8 (2.3-5.4)
	NRAS/KRAS	11.7%	3.7 (2.6-4.5)	3.4 (2.3-4.0)
	SETBP1	5.3%	2.4 (2.1-3.5)	2.0 (1.4-2.7)
	JAK2	3.7%	4.9 (2.9-8.3)	4.3 (2.5-6.8)
High-risk signatures	*TP53* + Complex Karyotype	2.1%	0.9 (0.7-1.3)	0.7 (0.6-1.1)
	NPM1, FLT3	2.5%	1.7 (1.0-2.6)	0.7 (0.5-1.2)

- 20% of patients could not be assigned to a specific genomic signature

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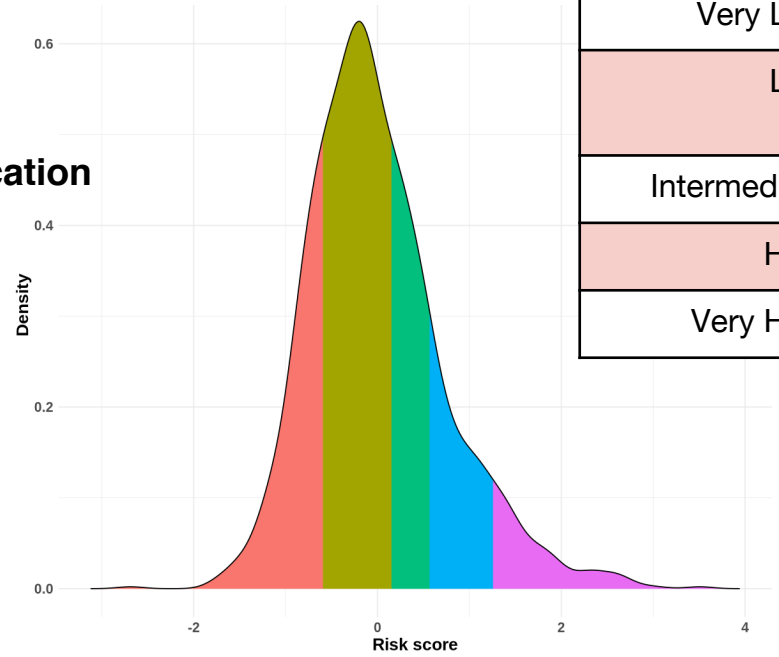
International CMML Prognostic Score (iCPSS)

- **Laboratory parameters:**
  - WBC
  - Hb
  - PLT
  - BM Blasts
- **CPSS cytogenetic stratification**
- **Mutational status (n=9)**
  - *ASXL1*
  - *DNMT3A*
  - *EZH2*
  - *RUNX1*
  - *SETBP1*
  - *STAG2*
  - *TET2*
  - *TP53*
  - *U2AF1*



Risk Class	Risk Score	%
Very Low	< -0.594	21%
Low	[-0.594, 0.147]	43%
Intermediate	[0.147, 0.566]	18%
High	[0.566, 1.258]	12%
Very High	≥1.258	7%

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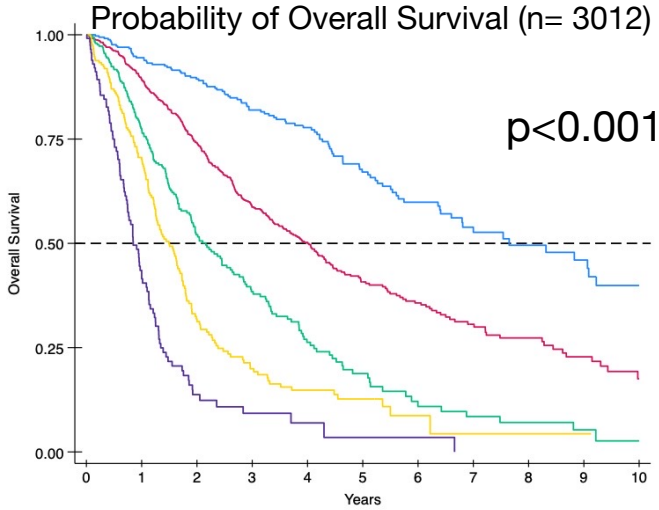
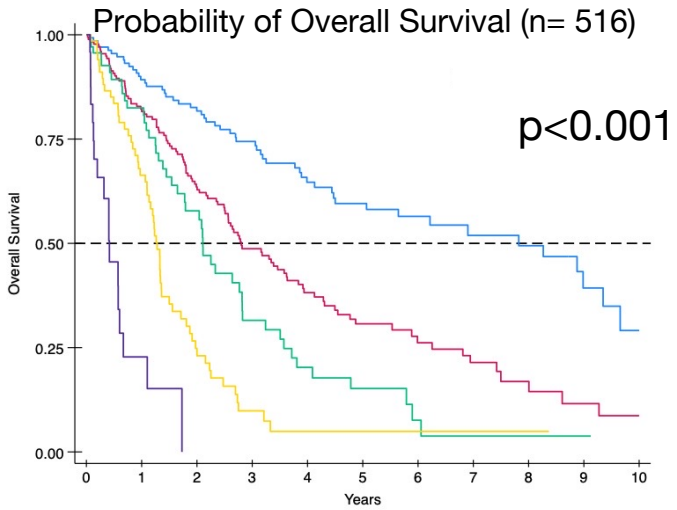
iCPSS and clinical outcomes in CMML





	C-INDEX
iCPSS	**0.75**
BLAST[1]	0.64
CPSS-mol[2]	0.63
GFM[3]	0.60
MMM[4]	0.61

Very Low Low Intermediate High Very High

	C-INDEX
iCPSS	**0.72**
BLAST[1]	0.69
CPSS-mol[2]	0.61
GFM[3]	0.59
MMM[4]	0.56

1: Tefferi et al. Blood 2025
2: Elena et al., Blood 2016, PMID 27385790
3: Itzykson et al., JCO 2013, PMID: 23690417
4: Patnaik et al., Leukemia 2013, PMID: 24695057

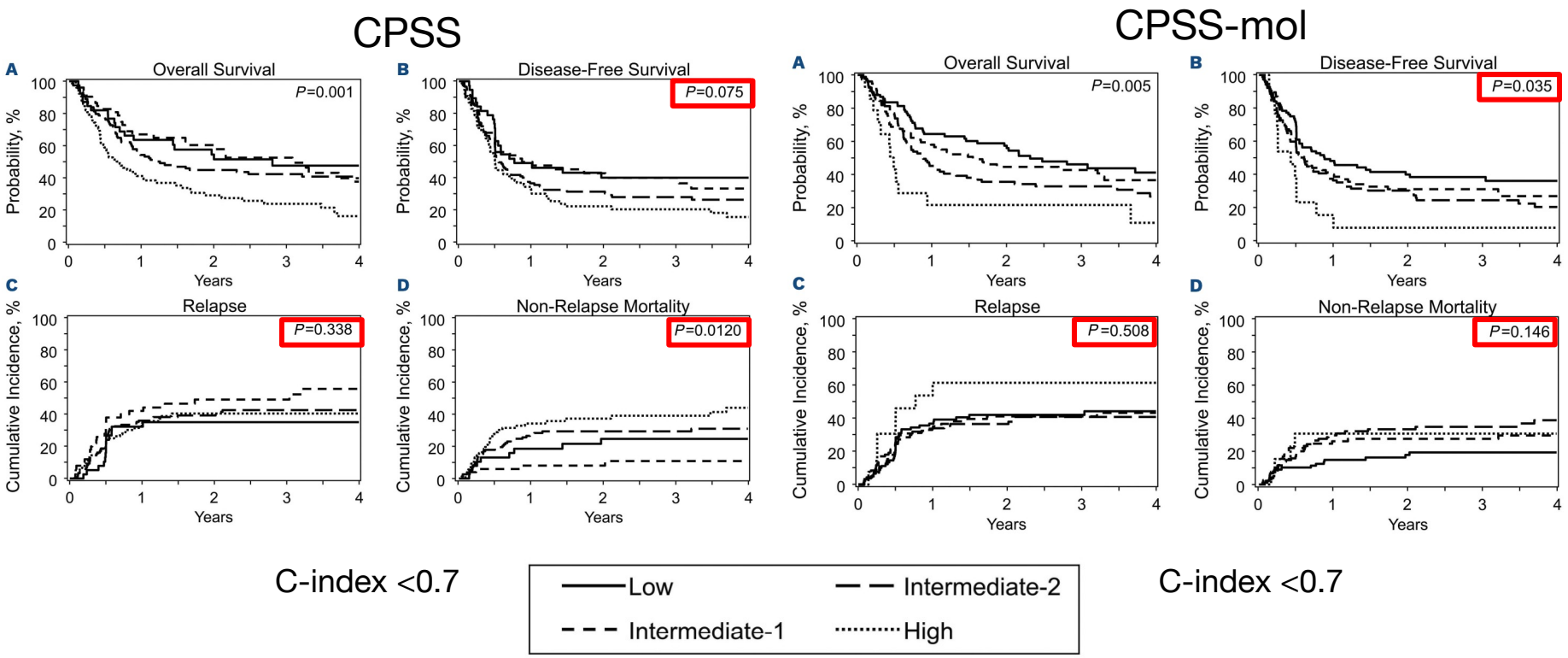
Lanino L, Blood 144 (2024) 1003–1008

Prognostic scores and transplant

- CMML is characterized by an increased rate of leukemic evolution and shorter survival.
- Allogeneic HSCT remains the only potential curative treatment for CMML. The toxicity associated with HSCT warrants a careful and personalized selection of potential candidates for the procedure.
- The optimal timing of HSCT in CMML patients remains an active area of research.
- Prognostic scores in CMML integrate minimal molecular information and offer poor predictive performances in the transplantation setting

Onida F,. Blood. 2024 May 30;143(22):2227-2244.

CPSS-Mol does not improve prognostic accuracy over CPSS after allogeneic transplant in CMML (n=313)



Mei M et al, Haematologica 2023;108(1):150-160

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Milan, Italy

A Decision Support System for Personalized Optimization of Hematopoietic Stem Cell Transplantation Timing in Chronic Myelomonocytic Leukemia

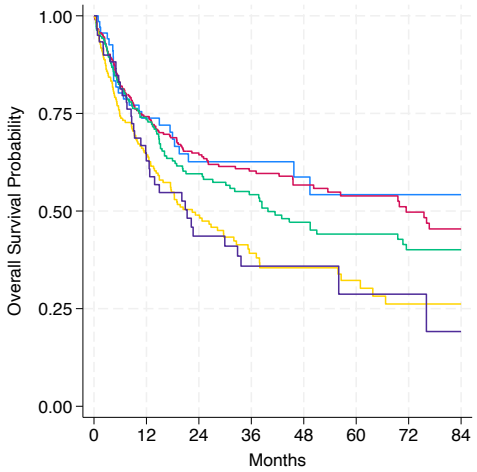
A Decision support system for personalized optimization of HSCT in CMML

Study population

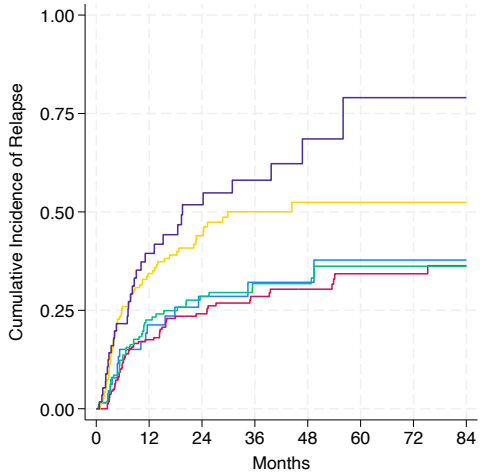
	Disease Natural History N = 2,184	Transplanted N = 829
Male sex	1,479 (68%)	545 (66%)
Age	73 (67-79)	61 (55-65)
WHO 2016		
CMML-0	1,185 (54%)	326 (39%)
CMML-1	644 (29%)	273 (33%)
CMML-2	355 (16%)	230 (28%)
WBC [x10^3/mmc]	10 (6-19)	12 (6-24)
Hb [g/dl]	11.1 (9.3-12.8)	10.5 (8.9-12.5)
Platelets [x10^3/mmc]	112 (63-196)	93 (51-176)
Bone Marrow Blasts [%]	4.0 (2.0-7.0)	6.0 (2.0-10.0)
CPSS-mol Risk Class		
Low	396 (18%)	56 (6.8%)
Intermediate-1	549 (25%)	176 (21%)
Intermediate-2	788 (36%)	363 (44%)
High	451 (21%)	234 (28%)
iCPSS Risk Class		
Very Low	435 (20%)	69 (8.3%)
Low	951 (44%)	298 (36%)
Intermediat	335 (15%)	193 (23%)
High	301 (14%)	207 (25%)
Very High	162 (7.4%)	61 (7.4%)
Conditioning		
Myeloablative		374 (45%)
Non-myeloablative		455 (55%)
Disease at HSCT		
AML		68 (8.2%)
CMML		761 (92%)

iCPSS for Transplant Outcomes (N=829)

Probability of Overall Survival



Cumulative Incidence of Relapse



	HR*	p
Very Low	0.97	0.9
Low	REF	-
Intermediate	1.32	0.004
High	1.76	<0.001
Very High	1.86	<0.001

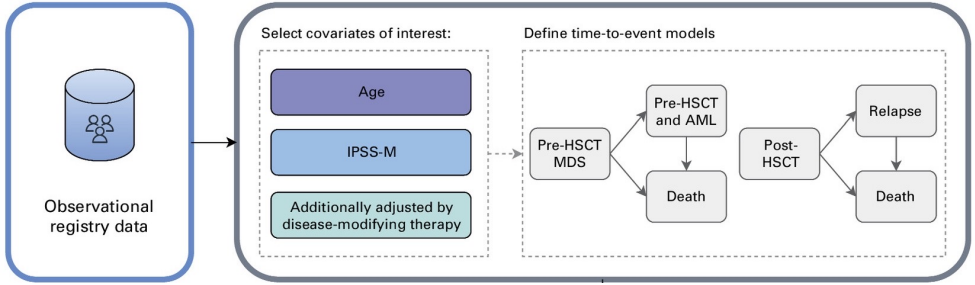
Very Low Low Intermediate High Very High

* HRs are from a MV model adjusted by donor, conditioning and response to treatment before HSCT

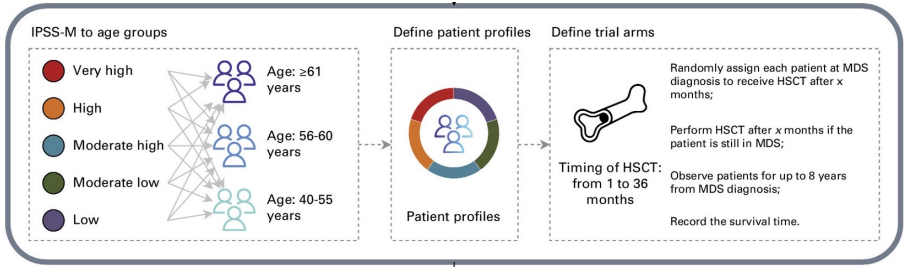
	HR*	p
Very Low	1.03	0.9
Low	REF	-
Intermediate	1.19	0.3
High	2.01	<0.001
Very High	2.65	<0.001

Clinical Decision Support System (CDSS)

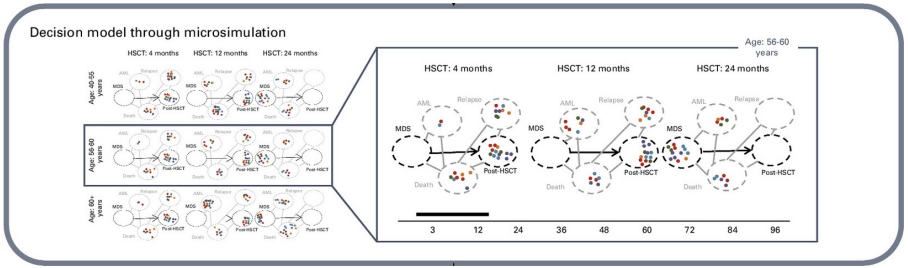
STEP 1 - Model of the disease natural history and the effect of treatment



STEP 2 Simulation of the target trial

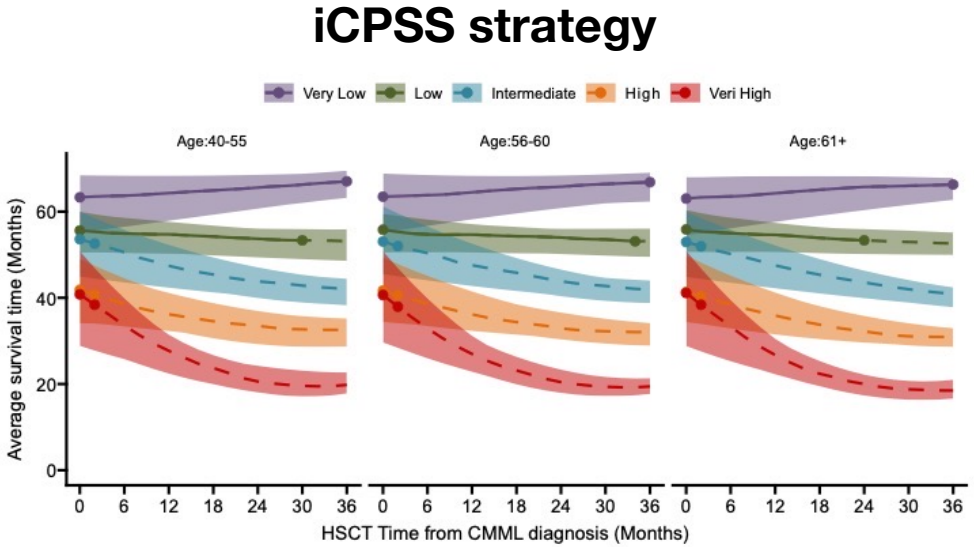


STEP 3 Scenario analysis - microsimulation



Tentori C et al. JCO 2024;42:2873-2886; Gregorio C et al. JCO CCI 2024, May; 8:e2300205.

Survival by iCPSS Policy

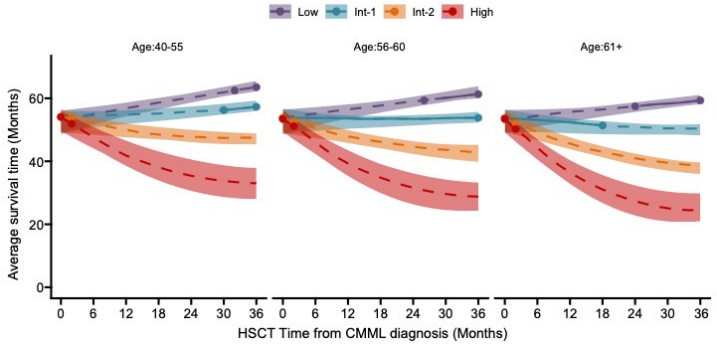


iCPSS	Optimal window HSCT
Very Low	Delayed
Low	Delayed
Intermediate	Immediate
High	Immediate
Very High	Immediate

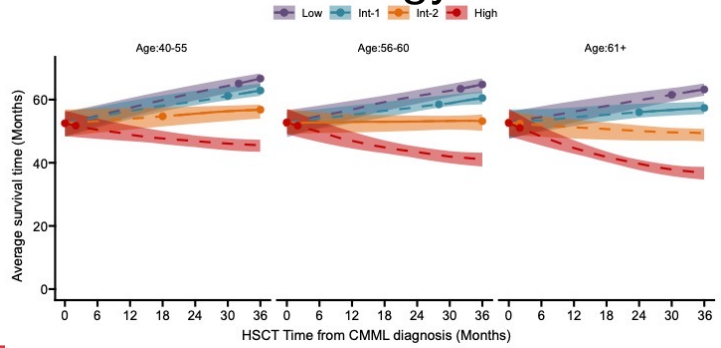
In patients at intermediate, high, and very high iCPSS risk, early transplant procedure was associated with a longer life expectancy

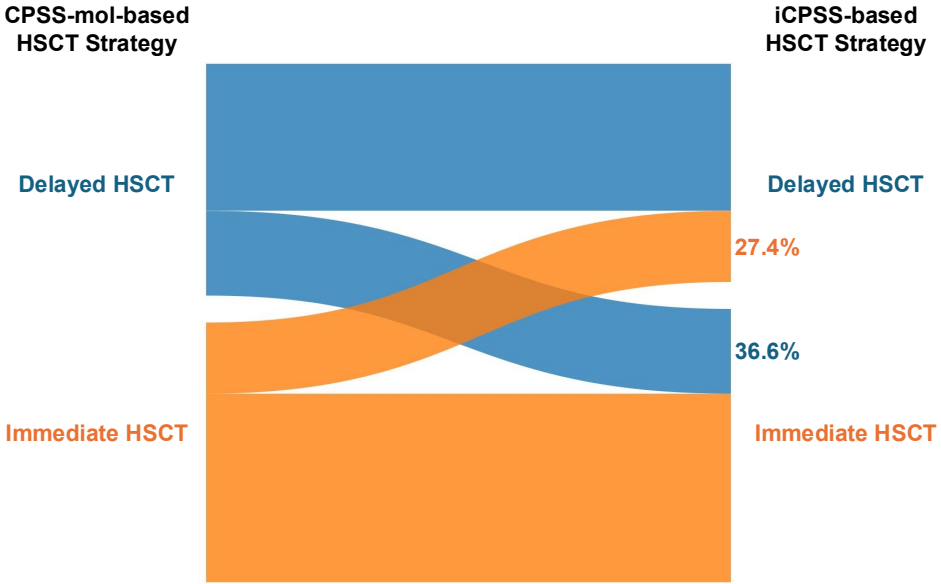
Comparison of iCPSS vs CPSS-mol transplantation policy

CPSS strategy



CPSS-mol strategy





The transplantation policy changed in 31% of cases after incorporating molecular features in the decision analysis.

Conclusion

- CMML is a rare, biologically complex disease leading to highly variable clinical outcomes.
- Despite the availability of several prognostic models, no model fully accounts for the disease's heterogeneity, especially in different treatment settings.
- The development of integrative models like BLAST-mol and iCPSS reflects the growing effort to refine risk stratification in CMML by combining clinical, cytogenetic, and molecular information.
- Optimal CMML management requires a personalized approach, integrating multiple layers of patient-specific data to inform risk assessment, treatment decisions, and long-term planning.

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