MPN- and MDS/MPN-unclassifiable

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Leukemia

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The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms

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Khoury JD et al. *Leukemia*. 2022 ;36 :1703-1719.

Arber DA, et al. *Blood*. 2022; 140: 1200-1228

International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data

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MPN- and MDS/MPN-unclassifiable

- The two classification proposals are not conflicting
- Minor differences, particularly regarding terminology
- In both classification proposals diagnosis is based on the integration of clinical, molecular and morphological features

(1) Khoury JD et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. *Leukemia*. 2022 ;36 :1703-1719.

(2) Arber DA, et al. International Consensus Classification of myeloid neoplasms and acute leukemia: integrating morphological, clinical, and genomic data. *Blood*. 2022; 140: 1200-1228

MPN, unclassifiable (ICC, 2022) / MPN, NOS (WHO 2022)

MPN-U / NOS: cases with clinical, morphological and molecular features of MPN but fail to meet the diagnostic criteria for a specific entity.

MPN-U / NOS can be subdivided in:

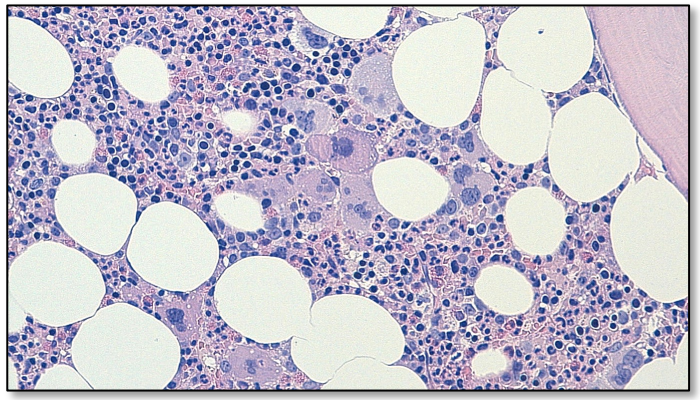
1. Early-stage MPN: in which the morphological and/or clinical features are not yet fully developed.

2. Advanced-stage MPN: in which stromal changes (myelofibrosis, osteosclerosis) mask the underlying disorder.

3. MPN with coexisting neoplastic or inflammatory disorder.

MPN, unclassifiable (ICC, 2022) / MPN, NOS (WHO 2022)

Early-stage MPN-U

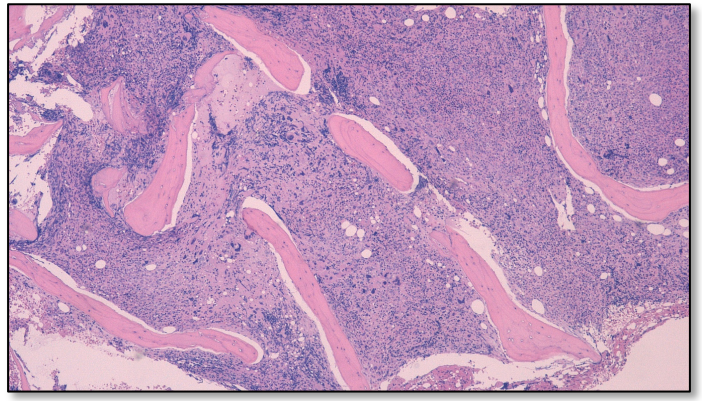


Pre-PMF vs ET

Masked PV

MPN with SVT

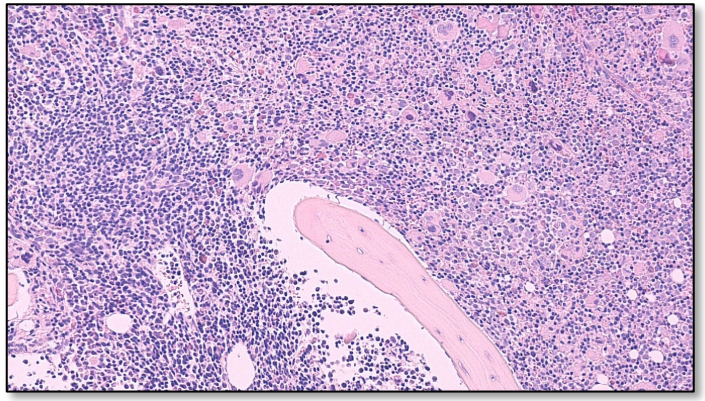
Advanced stage MPN-U



Overt PMF vs post ET-MF

Overt PMF vs post PV-MF

MPN-U + …..



MPN + NHL

MPN + SM

MPN + solid tumors

Thiele J et al. Am J Hematol. 2023 98:544-545; Gianelli U. et al. Virchows Arch. 2023 482: 53-68

The **clinical presentation** is variable:

- MPN-U in early stages may display increased blood cell counts (thrombocytosis and/or leukocytosis and/or erythrocytosis) without splenomegaly or hepatomegaly;

- MPN-U in advanced stages are characterized by cytopenia, and organomegaly.

Table 1 Clinical–pathological features of 71 cases of myeloproliferative neoplasm, unclassifiable

Features	*Patients*
Age (years); median (range)	61 (14–91)
Male sex; no. of cases (%)	31 (43.7%)
Hemoglobin (g/dl); median (range)	14.3 (8.2–17.3)
Hematocrit (%); median (range)	42.5 (22.7–52.7)
WBC count (x10^9/l); median (range)	8.15 (3.4–52.6)
PLT count (x10^9/l); median (range)	577 (91–1547)
LDH (IU/l); median (range)	353 (127–839)
Serum EPO (mIU/ml); median (range)	4.00 (1.00–37.3)
Circulating CD34+ cells (/µl); median (range)	3 (1–552)
Palpable splenomegaly; no. of cases (%)	31 (43.7%)
Cytogenetic abnormalities; no. of cases (%)	4 (5.6%)
Molecular analyses	
*JAK2*V617F; no. of cases (%)	51 (71.8%)
JAK2 allele burden (%); median (range)	20.9 (3.8–83.0)
*MPL*W515L; no. of cases (%)	2 (2.8%)
CALR mutation; no. of cases (%)	8 (11.3%)
Type 1 mutation; no. of cases (%)	4 (5.6%)
Type 2 mutation; no. of cases (%)	2 (2.8%)
Other mutations; no. of cases (%)	2 (2.8%)
Triple negative; no. of cases (%)	2 (2.8%)

Gianelli U et al. Mod Pathol 2017

Diagnostic criteria for MPN-U, ICC 2022

1. Clinical and hematological features of a myeloproliferative neoplasm are present
2. JAK2, CALR, or MPL mutation or presence of another clonal marker
3. Diagnostic criteria for any other MPN, MDS, MDS/MPN or BCR::ABL1-positive CML are not met

In cases presenting with ***BM fibrosis reactive causes must be excluded*** (infection, autoimmune disorder or another chronic inflammatory condition, lymphoid neoplasm, metastatic malignancy, or toxic myelopathy).

It is recommended to ***use highly sensitive assays*** for ***JAK2*** (sensitivity level, 1%) and ***CALR and MPL*** (sensitivity level 1% to 3%); in negative cases, consider searching for noncanonical JAK2 and MPL mutations.

Assessed by cytogenetics or sensitive NGS techniques; ***detection of mutations associated with myeloid neoplasms*** (eg, ASXL1, EZH2, IDH1, IDH2, SF3B1, SRSF2, and TET2 mutations) supports the clonal nature of the disease.

Arber DA, et al. *Blood*. 2022; 140: 1200-1228

Diagnostic criteria for MPN, NOS - WHO 2022

Requires the presence of all 3 criteria:
1. Presence of features of an MPN.
2. WHO criteria for any other MPN, MDS, MDS/MPN, or BCR::ABL1–positive CML are not met, negative for *PDGFRA, PDGFRB, FGFR1, JAK2* fusions, *ETV6::ABL1*, and other *ABL1* rearrangements.
3. Presence of driver mutations such as *JAK2, CALR*, or *MPL* mutation, or another clonal marker.
Requires the absence of both these criteria:
1. Insufficient clinical data or inadequate bone marrow specimen for accurate evaluation and classification
2. Recent history of cytotoxic or growth factor therapy, particularly when dysplastic features are seen.

Khoury JD et al. *Leukemia*. 2022 ;36 :1703-1719.

Diagnostic criteria for MPN, NOS - WHO 2022

MPN features include either one of the following:

Clinical: splenomegaly, atypical thrombosis, leukocytosis, in the absence of significant monocytosis and significant eosinophilia (not meeting criteria for CEL)

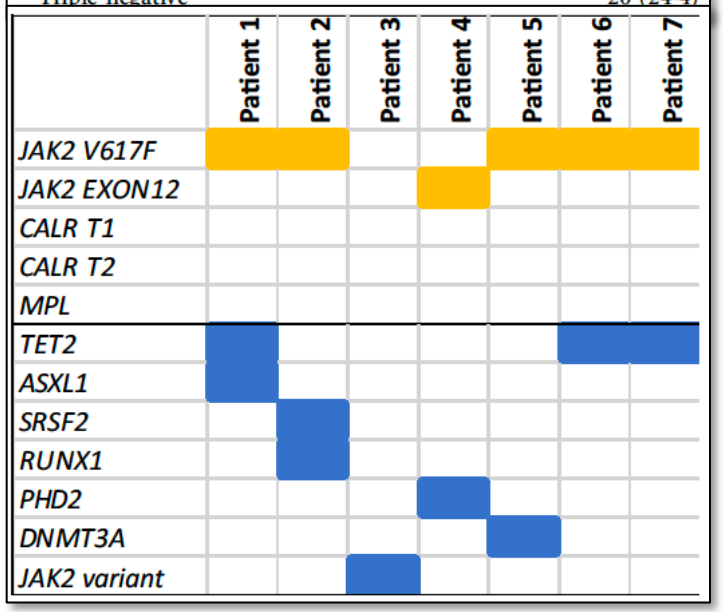
Morphological: bone marrow morphology features of atypical megakaryocytic hyperplasia in a hypercellular marrow, panmyelosis, in the absence of dysplastic features

In the **pathology report**, it is important to:

1. describe the morphological findings
2. summarize the reasons for the difficulty in the classification
3. specify any particular subtypes that can be excluded

WHO Classification of Tumours Editorial Board. Haematolymphoid tumours [Ibeta V2 ahead of print]

BM cellularity	73 (89)	
High		49 (67·1)
Normal		22 (30·1)
Reduced		2 (2·7)
Panmyelosis		11(15)
Megakaryopoiesis	47 (51)	
Increased		47 (100)
Clustered		39 (82·9)
Pleiomorphic		39 (82·9)
WHO Fibrosis Grade	73 (89)	
0		23 (31·5)
1		39 (53·4)
2		9 (12·3)
3		2 (2·7)
LDH, ui/l, median	72 (87·8)	249·5
Driver molecular status, *n* (%)	82 (100)	
Mutated *JAK2 V617F*		44 (53.7)
Mutated *JAK2 exon 12*		2 (2·4)
Mutated *CALR Type1*		7 (8·5)
Mutated *CALR Type2*		4 (4·8)
Mutated *cMPL*		5 (6·1)
Triple negative		20 (24·4)



Clinicopathological characterisation of myeloproliferative neoplasm-unclassifiable (MPN-U): a retrospective analysis from a large UK tertiary referral centre

82 MPN-U pts; age (median): 49 (13–79) yrs; F (56%) M (44%)

CBC

Thrombocytosis (78%); PTL (median) 650 x 10^9/L

Hb levels and WBC counts were within the normal range

Symptoms

Splenomegaly (27%)

Pruritus (36%)

Constitutional symptoms (29%).

Transfusion dependency (24%).

Blood film morphology

leucoerythroblastic features (7%)

'tear drop' poikilocytes (18%)

Large granular lymphocytes in 20%.

Deschamps P et al. Br J Hematol 2021

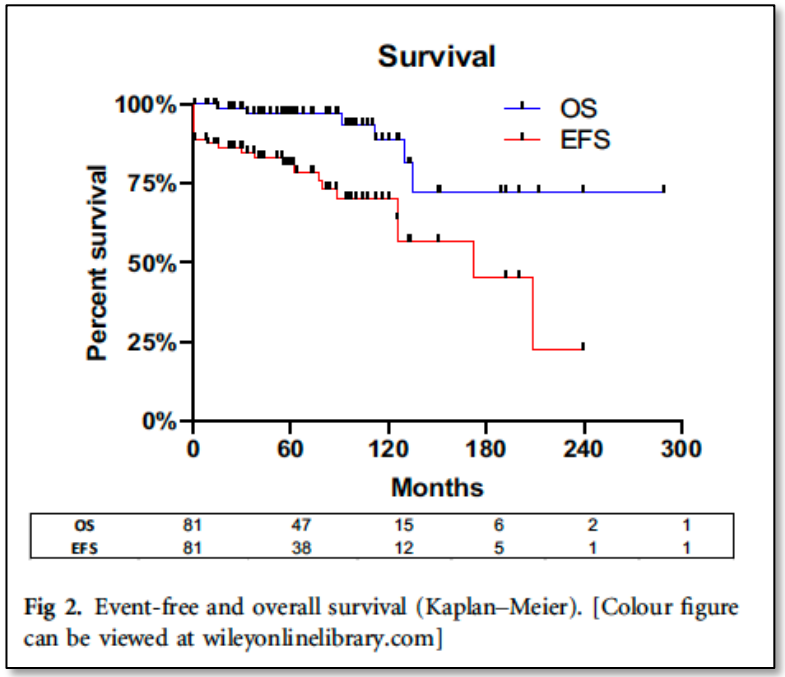
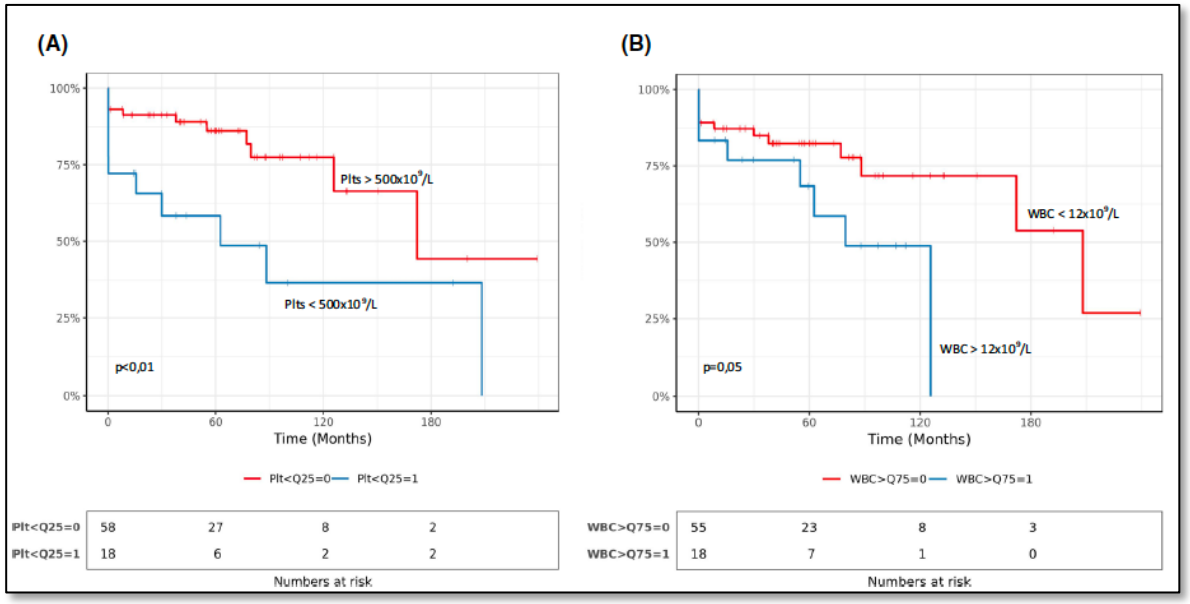


Fig 2. Event-free and overall survival (Kaplan–Meier). [Colour figure can be viewed at wileyonlinelibrary.com]



Median EFS was 11.25 years (Fig. 2).

Seven patients (85%) progressed to AP or BP with a median time to transformation of 882 (156 – 1839) months.

Median 10-year estimated OS was 88.8%

Parameters associated with worse EFS were a platelet count at presentation of <500 x 10^9/L and leukocytosis ≥12 x10^9/L

Deschamps P et al. Br J Hematol 2021

Myelodysplastic/myeloproliferative neoplasm, NOS (MDS/MPN-NOS)

A myeloid neoplasm with dysplastic and proliferative features that does not meet the criteria for other defined MDS/MPN entities.

Clinical features can include MPN-like symptoms (weight loss, night sweats, organomegaly and thromboembolic complications), and MDS-like symptoms (anaemia, fatigue, dyspnea, infections, and bleeding).

CBC: hybrid features with significant and sustained cytosis (leukocytosis, thrombocytosis in about 20%) and cytopenias (anaemia, thrombocytopenia, and rarely neutropenia).

Relatively high frequencies of *TET2, NRAS, RUNX1, CBL, SETBP1* and *ASXL1* mutations have been reported

WHO Classification of Tumours Editorial Board. Haematolymphoid tumours [Ibeta V2 ahead of print]

Diagnostic criteria for MDS/MPN, NOS – ICC 2022

Myeloid neoplasm with mixed myeloproliferative and myelodysplastic features, not meeting the WHO criteria for any other MDS/MPN, MDS or MPN.
Cytopenia (thresholds same as for MDS)
Blasts < 20% in PB and BM
PTL ≥ 450 x 10^9/L and/or WBC ≥ 13 x 10^9/L
Presence of clonality: demonstration of a clonal cytogenetic abnormality and/or somatic mutation(s). If clonality cannot be determined, the findings have persisted and all other causes (e.g., history of cytotoxic or growth factor therapy or other primary causes that could explain the myelodysplastic/myeloproliferative features) have been excluded
No BCR::ABL1 or genetic abnormalities of myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions; no t(3;3) (q21.3;q26.2), inv(3)(q21.3;q26.2)

Arber DA, et al. *Blood*. 2022; 140: 1200-1228

WBC count (× 10^9/l)				
Median	17 (1–141)			
<13	39	46%	11.5	0.567
⩾13	15	18%	17.5	
⩾25	31	36%	12.4	
HGB (g/dl)				
Median	10 (5–15)			
<10	39	46%	12.4	0.504
⩾10	46	54%	12.4	
PLT count (× 10^9/l)				
Median	85 (6–1168)			
<450	74	87%	11.9	<0.001
⩾450	11	13%	52.5	
PB blast %				
Median	1 (0–16)			
⩾1%	48	56%	11.7	0.023
None	37	44%	23.1	
BM blast %				
Median	3 (0–17)			
⩽5%	60	71%	15.7	0.017
6–10%	17	20%	11.7	
>10%	8	9%	4.5	

Cytogenetics				
Diploid	42	49%	15.7	0.224
+8	13	15%	11.9	
Complex	10	12%	8.3	
Other	20	23%	24.7	
JAK2-V617F				
Median allele burden:	48 (1–95)			
Positive	17	20%	8.9	0.251
Negative	39	46%	17.7	
Unknown	29	34%		

85 MDS/MPN-U patients

Age > 60 years	92%
Anemia (Hb< 10g/dL)	46%
Leukocytosis (> 13 x 10^9/L)	54%
Thrombocytosis (>450 x 10^9/L)	13%
Splenomegaly	35%

Median OS was 12.4 months (0.3–138.7 months).

Four clinical variables associated with favorable outcome included: age < 60 years, thrombocytosis, lack of circulating blasts and <5% BM blasts

In multivariate analysis only thrombocytosis > 450 x 10^9/L retained prognostic significance

Di Nardo CD et al. Leukemia 2014

(MDS/MPN-U): Mayo Clinic - Moffitt Cancer Center study

135 patients

Splenomegaly 36%

Abnormal karyotype 49%:

trisomy 8, monosomy 7/deletion 7q, deletion 20q, complex karytoype (11%)

NGS

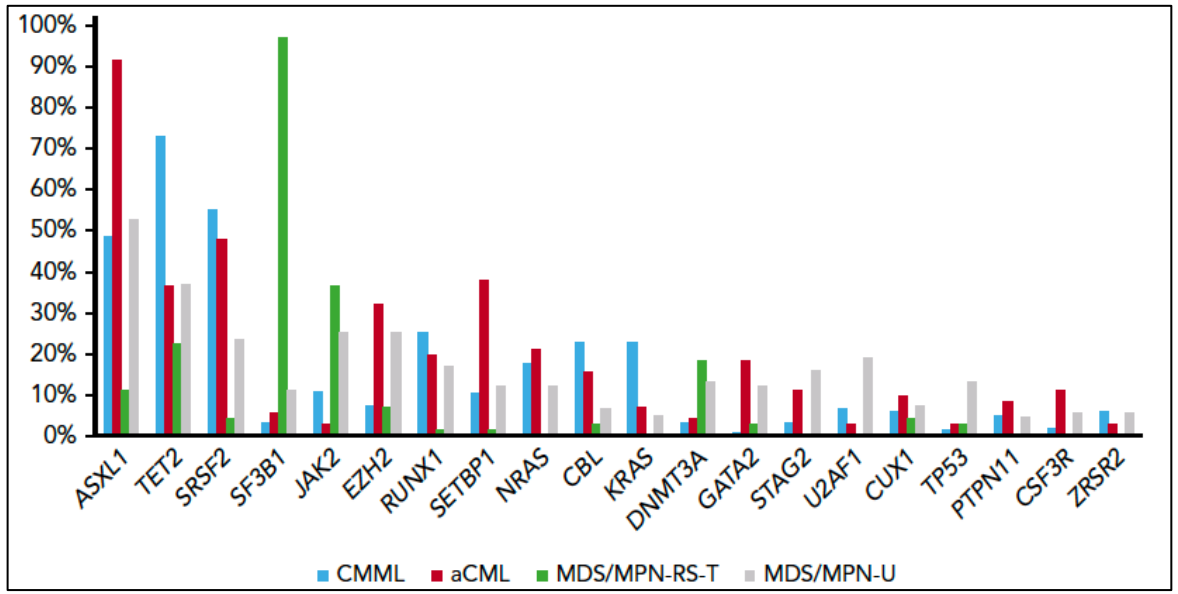
ASXL1mt (56%), SRSF2mt (n=23, 37%), SETBP1mt (n=13, 21%), JAK2 V617Fmt (n=12, 19%), NRASmt (n=9, 15%) and TET2mt (n=8,13%)

At a last median follow-up time of 61 months, 49 (36%) patients were alive and 21 (16%) leukemic transformations were documented.

Variable; Median value (range or %)	All ($n = 135$)
Age (years)	70 (37–93)
No. of males	87 (64)
Hb; gm/dl	9.7 (5.8–16.2)
WBC count $\times 10^9$ per liter	12.8 (0.9–69.1)
ANC $\times 10^9$ per liter	8.15 (0–78.2)
Platelet count $\times 10^9$ per liter	132 (8–1371)
BM blast%	2 (0–18)
BM blast% > 5	24 (19)
PB blast%	0 (0–18)
PB blast% > 1	23 (18)
[a]BM ring sideroblast%	0 (0–80)

Mangaonkar A.A. et al. Leukemia (2020) 34:656–661

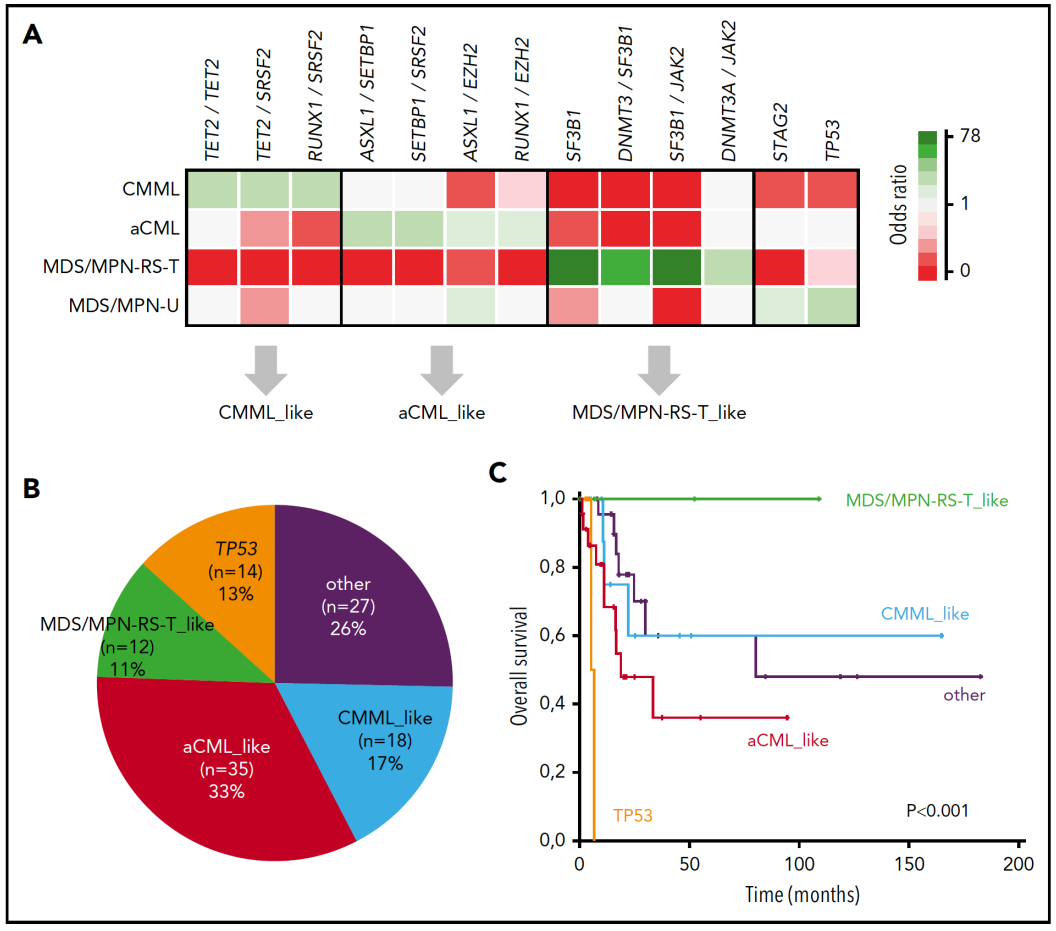
(*)MDS/MPN-U (n = 106)



Palomo L. et al. Blood 2020

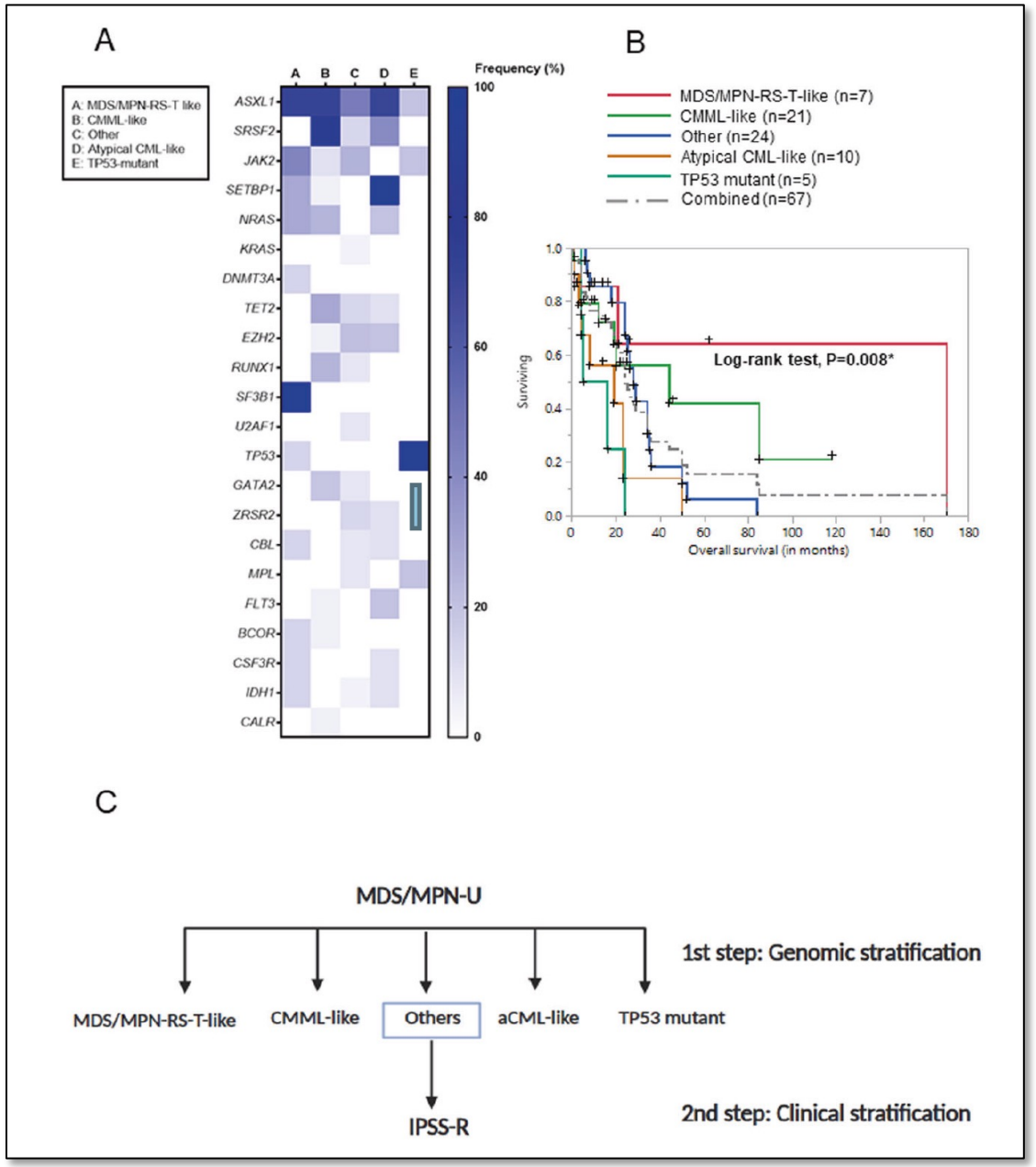
- According to the molecular profile MDS/MPN-U cases were categorized as “CMMLlike” (17%), “aCML-like”(33%) and MDS/MPN RS-T–like”(11%).
- In addition, 13% of the patients were categorized as “TP53”, because they were characterized by the presence of either mono- or biallelic TP53 mutations.
- The rest of the patients (26%), categorized as “others” did not show distinctive gene signatures but were enriched in U2AF1, JAK2 and ASXL1
- Molecular subtypes of MDS/MPN-U displayed hematological parameters in accordance with their phenotypic group:
  - CMML-like cases had higher monocyte count
  - aCML-like cases had higher WBC counts
  - MDS/MPN RS-T–like cases had a higher percentage of ring sideroblasts.
  - TP53 cases had more anemia and higher BM blasts percentage
  - “others” patients were characterized by thrombocytosis, which correlated with the presence of JAK2 mutations.

Molecular classification has prognostic significance



Palomo L. et al. Blood 2020

Adopted in WHO Classification of Tumours Editorial Board. Haematolymphoid tumours [Ibeta V2 ahead of print]



Mangaonkar AA et al. Leukemia 2021

Conclusion

MPN-U /NOS and MDS/MPN, NOS categories shouldn't be considered as a basket in which to put difficult cases.

Specific positive and negative diagnostic criteria should be applied to classify a patient into these categories and follow-up is sometimes helpful to clarify the diagnosis.

Pathologists should provide clinicians a detailed pathologic report of the bone marrow aspirate and biopsy, summarizing the reasons for the difficulty in the classification and specifying any subtypes that can be excluded.