EBMT Registry

MDS/MPN overlap syndromes

Guide to the completion of the EBMT data collection form: MDS/MPN_v2.0

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EBMT Registry

EBMT Clinical Research & Registry Department

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Introduction

Please make sure you have already checked the **Introduction to the EBMT Registry Completion Guidelines** document latest version available under *Manuals and Reference Documents* section on EBMT website.

MDS/MPN overlap syndromes

MDS/MPN overlap syndromes are a group of chronic clonal myeloid malignancies in which there are features of both MDS and MPN at the time of presentation. This category is composed of the following major myeloid disorders: chronic myelomonocytic leukaemia (CMML), MDS/MPN with SF3B1 mutation and thrombocytosis and MDS/MPN with neutrophilia and MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T). Myeloid disease that shows features of both MDS and MPN but does not meet the criteria for any of the major MDS/MPN entities is designated as MDS/MPN-NOS (not otherwise specified).

All MDS/MPN subclassifications are negative for BCR::ABL1 fusions, or rearrangements involving PDGFRA, PDGFRB, FGFR1 and JAK2 and have <20% blasts in the peripheral blood (PB) and in the bone marrow (BM).

This form must be completed for all patients whose primary disease for which the HCT/CT treatment is being given is MDS/MPN. When the MDS/MPN has transformed to acute myelogenous leukaemia (AML) before HCT/CT, please complete both the MDS/MPN diagnosis form and the Acute Leukaemias diagnosis form.

No data items should be left blank unless specifically stated in the definition.

Disease

Date of diagnosis

Report the date of the first pathological diagnosis of the disease. This is the date when the sample was collected for examination or (in its absence) the date indicated by a physician within the patient's medical record.

MDS/MPN transformed into Acute Leukaemia and treatment was done for Acute Leukaemia?

MDS/MPN can progress through different phases (subclassifications) from the time of diagnosis to transplantation. One of these phases can be AML.

If the patient is being transplanted for AML that has transformed from MDS/MPN, select **Yes** and complete the Acute Leukaemias diagnosis form in addition to the current form. Otherwise, check the **No** option.

Classification (WHO 2022)

According to the WHO 2022 (1) classification there are five subclassifications of the MDS/MPN overlap syndrome:

Chronic myelomonocytic leukaemia (CMMoL, CMML):

Prerequisite criteria

1. Persistent absolute (≥0.5 × 10^9/L) and relative (≥10%) peripheral blood monocytosis.
2. Blasts constitute <20% of the cells in the peripheral blood and bone marrow.[a]
3. Not meeting diagnostic criteria of chronic myeloid leukaemia or other myeloproliferative neoplasms.[b]
4. Not meeting diagnostic criteria of myeloid/lymphoid neoplasms with tyrosine kinase fusions.[c]

Supporting criteria

1. Dysplasia involving ≥1 myeloid lineages.[d]
2. Acquired clonal cytogenetic or molecular abnormality.
3. Abnormal partitioning of peripheral blood monocyte subsets.[e]

Requirements for diagnosis

- Pre-requisite criteria must be present in all cases.
- If monocytosis is ≥ 1 × 10^9/L: one or more supporting criteria must be met.
- If monocytosis is ≥0.5 and <1 × 10^9/L: supporting criteria 1 and 2 must be met.

[a]Blasts and blast equivalents include myeloblasts, monoblasts and promonocytes.

[b]Myeloproliferative neoplasms (MPN) can be associated with monocytosis at presentation or during the course of the disease; such cases can mimic CMML. In these instances, a documented history of MPN excludes CMML. The presence of MPN features in the bone marrow and/or high burden of MPN-associated mutations (JAK2, CALR or MPL) tends to support MPN with monocytosis rather than CMML.

[c]Criteria for myeloid/lymphoid neoplasms with tyrosine kinase fusions should be specifically excluded in cases with eosinophilia.

[d]Morphologic dysplasia should be present in ≥10% of cells of a haematopoietic lineage in the bone marrow.

[e]Based on detection of increased classical monocytes (>94%) in the absence of known active autoimmune diseases and/or systemic inflammatory syndromes.

MDS/MPN with SF3B1 mutation and thrombocytosis:

- Platelet count ≥ 450×10^9/L.
- 15% ring sideroblasts in the BM or >5% with SF3B1 mutation.
- Presence of megakaryocytic atypia resembling ET or MF.

MDS/MPN with neutrophilia (Atypical CML (t(9;22) negative and BCR::ABL1 negative):

- WBC count > 13×10^9/L with increased and dysplastic neutrophils (immature myeloid cells ≥ 10%).
- No or minimal absolute basophils and monocytosis.
- Hypercellular BM with granulocytic proliferation and dysplasia.

MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T):

- Platelet count ≥ 450×10^9/L.
- 15% ring sideroblasts in the BM or >5% with wild-type SF3B1.
- Presence of megakaryocytic atypia resembling ET or MF.

MDS/MPN-NOS (not otherwise specified):

Myeloid neoplasm with mixed MDS and MPN features, not meeting WHO criteria for other MDS/MPN overlap neoplasms, MDS or MPN.

CMML subtype

The prototype and most common MDS/MPN is chronic myelomonocytic leukaemia (CMML), which is characterised by sustained peripheral blood monocytosis and various combinations of somatic mutations involving epigenetic regulation, spliceosome, and signal transduction genes.

Two main phenotypic types of CMML can be distinguished:

CMML subtype	**Subtyping criteria**
Myelodysplastic (MD-CMML)	WBC < 13×10^9/L
Myeloproliferative (MP-CMML)	WBC > 13×10^9/L

Table 1. CMML subtypes.

Patients with myeloproliferative type tend to have bulkier splenomegaly and more often have extramedullary infiltrations. MP-CMML is commonly associated with activating RAS pathway mutations and adverse clinical outcomes. Even though no difference exists with regard to the AML transformation rate, patient life expectancy is generally shorter in MP-CMML than in MD-CMML.

CMML subgroup

According to the WHO 2022 (1), CMML can be further subclassified according to the percentage of blasts in peripheral blood and in bone marrow into CMML-1 and CMML-2:

CMML subgroup	**Subgrouping criteria**
CMML-1	<5% blasts in the blood and <10% blasts in the bone marrow
CMML-2	5-19% blasts in the blood and 10-19% blasts in the bone marrow

Table 2. WHO 2022 CMML subgroups.

Therapy-related MDS/MPN

Indicate if MDS/MPN developed due to medical treatment (therapeutic agents or radiation).

CPSS (for CMML only)

The CMML-specific prognostic scoring system (CPSS) combines clinical and cytogenetic data. Patients can be categorised into 4 risk groups according to following points:

- CMML-2 according to WHO 2022 (1 point)
- WBC ≥13x10^9/L (1 point)
- RBC transfusion dependency (1 point)
- Cytogenetic risk group:
    - Low (normal and -Y) (0 points)
    - Intermediate (other abnormalities) (1 point)
    - High (trisomy 8, complex and abnormalities of chromosome 7) (2 points)

Risk category	**Risk score**
Low	0
Intermediate-1	1

Intermediate-2	2-3
High	4-5

Table 3. CPSS risk groups.

CPSS-Mol (for CMML only)

The CMML-specific prognostic scoring system Moleculair (CPSS-Mol) combines clinical, cytogenetic and molecular data. Patients can be categorised into 4 risk groups according to following points:

- WBC ≥13x10^9/L (1 point)
- Bone marrow blasts (%) ≥ 5% (1 point)
- RBC transfusion dependency (1 point)
- Cytogenetic risk group:
    - Low (normal and -Y) (0 points)
    - Intermediate (other abnormalities) (1 point)
    - High (trisomy 8, complex and abnormalities of chromosome 7) (2 points)
- ASXL1 mutation (1 point)
- NRAS mutation (1 point)
- RUNX1 mutation (2 points)
- SETBP1 mutation (1 point)

Please see the table below for the risk groups. The score can be calculated with an online tool, such as:

https://qxmd.com/calculate/calculator_609/cmml-cpss-mol

Risk category	**Risk score**
Low	0
Intermediate-1	1
Intermediate-2	2-3
High	≥4

Table 4. CPSS-Mol risk groups.

Chromosome analysis

Chromosome analysis done before HCT/CT/IST treatment

In this section describe the results of all chromosome analyses (all methods including FISH) performed at/after diagnosis but before the HCT/CT/IST treatment. If there were multiple chromosome analysis tests done on different dates, the results can be registered separately along with the test date.

Indicate if chromosome analysis was done or not before the HCT/CT/IST treatment. Check **Unknown** if it is not known whether it was performed.

Output of analysis

Indicate if the output of the chromosome analysis will be reported as **separate abnormalities** or as a **full karyotype**.

What were the results?

Normal - the chromosome analysis has been performed and the results have been found normal

Abnormal - the chromosome analysis has been performed and abnormalities have been found. In addition, indicate the total number of different abnormalities present (**number of abnormalities present**).

Failed - the chromosome analysis was done but failed

Date of chromosome analysis

Indicate the date of the chromosome analysis. If the date is unavailable, select **Unknown**.

Chromosome analysis details

Indicate for each abnormality in the table whether it was **Absent, Present** or **Not evaluated**.

If a chromosome abnormality was checked, but not listed as an option in the table, select **Other** and specify the abnormality, marking whether it was **Absent** or **Present**.

Transcribe the complete karyotype

if it is not possible to report the chromosome analysis results as per abnormalities table please enter the complete karyotype. Describe all abnormalities according to the ISCN karyotype nomenclature. This notation includes the total number of chromosomes, the sex chromosomes, and any extra, missing or mutated autosomal chromosomes. For example, **47, XY, +18** indicates that the patient has 47 chromosomes, is a male, and has an extra autosomal chromosome 18.

Molecular marker analysis

Molecular markers analysis done before HCT/CT/IST

In this section, describe the results of all molecular marker analyses (performed at/after diagnosis but before HCT/CT/IST). If there were multiple molecular marker analyses tests done on different dates, the results can be registered separately along with the test date.

Indicate if molecular marker analysis was done or not before HCT/CT/IST. Check **Unknown** if it is not known whether it was performed.

Date of molecular marker analysis

Indicate the date of the molecular marker analysis. If there were multiple molecular tests done on different dates, the results can be registered separately along with the test date.

Molecular marker analysis details

If molecular marker analysis was performed, indicate for each marker in the table whether it was **Absent, Present** or **Not evaluated**.

If a molecular marker was evaluated, but not listed as an option in the table, select **Other** and specify the marker, indicating whether it was **Absent** or **Present**.

TP53 mutation

If TP53 mutation is present, indicate the mutation type if known. A TP53 mutation is considered a multi hit if it fulfils one of the following criteria

- 2 or more distinct mutations of TP53 with a VAF of ≥ 10%
- 1 mutation and 1 deletion involving the TP53 locus
- 1 mutation with VAF ≥ 50%
- 1 mutation with complex karyotype

A TP53 mutation is considered single hit if either one of the following criteria is fulfilled:

- a single TP53 mutation with VAF < 50%
- loss of 17p13 involving TP53 locus without TP53 mutations

If the lab report does not specify the type, select **Unknown**.

Bibliography

1. Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, Apperley JF, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms. Leukemia. 2022;36:1703–19. doi: 10.1038/s41375-022-01613-1.