

Combined myelodysplastic syndrome/myeloproliferative neoplasm (MDS/MPN)

**Guide to the completion of the EBMT data collection
form: MDS/MPN_v1.0**

21 August 2023

EBMT Registry

EBMT Clinical Research & Registry Department



**Co-funded by
the European Union**

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Introduction

Myelodysplastic syndrome/myeloproliferative neoplasm (MDS/MPN) 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 was originally composed of the following major myeloid disorders: chronic myelomonocytic leukemia (CMML), juvenile myelomonocytic leukemia (JMML), MPN-MDS with ring sideroblasts and atypical chronic myeloid leukemia (aCML). 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 myelodysplastic/myeloproliferative neoplasm, unclassifiable (MDS/MPN-U).

All MDS/MPN subclassifications are negative for BCR::ABL1 fusions, or rearrangements involving PDGFRA, PDGFRB, FGFR1 and PCM1-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 reported treatment is being given is MDS/MPN. When the MDS/MPN has transformed to acute myelogenous leukaemia (AML) before HCT/CT/IST, please complete both the MDS/MPN diagnosis form and the Acute Leukaemias diagnosis form. In addition, the MDS/MPN diagnosis form can be completed if it was requested for specific studies.

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

Disease

1. Date of diagnosis

Report the date of the first pathological diagnosis of the disease. Add 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.

2. 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.

3. MDS/MPN Classification

According to the WHO 2016 (1) classification there are five subclassifications of the MDS/MPN overlapping syndrome:

MPN/MDS subclassification	WHO 2016 diagnostic criteria
Chronic myelomonocytic leukaemia (CMMoL, CMML)	<p>Persistent PB absolute and relative monocytosis ($\geq 1 \times 10^9/L$ and $\geq 10\%$).</p> <p>Dysplasia in ≥ 1 lineage, if no dysplasia, then must include an acquired clonal cytogenetic or molecular genetic abnormality. Any genetic abnormality would be indicative of clonality (e.g. some patients have only JAK2 or CBL or RUNX1 or N-KRAS mutations).</p>
Juvenile myelomonocytic leukaemia (JCMMoL, JMML, JCML, JCMML)	<p>PB monocyte count $\geq 1 \times 10^9/L$.</p> <p>Splenomegaly. Genetic features (must include 1 of the following): somatic mutation in PTPN11¹, KRAS³, or NRAS³; diagnosis of neurofibromatosis-1 or NF1 mutation; or germline CBL mutation and loss of heterozygosity of CBL.</p> <p>If no genetic features then, must have a clonal chromosomal abnormality or all of the following: GM-CSF hypersensitivity, hyperphosphorylation of STAT5, fetal hemoglobin increased for age, myeloid or erythroid precursors on PB smear.</p>
Atypical CML (t(9;22) negative and BCR-ABL1 negative)	<p>WBC count $> 13 \times 10^9/L$ with increased and dysplastic neutrophils (immature myeloid cells $\geq 10\%$).</p> <p>No or minimal absolute basophils and monocytosis.</p> <p>Hypercellular BM with granulocytic proliferation and dysplasia.</p>
MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)	<p>Platelet count $\geq 450 \times 10^9/L$.</p> <p>15% ring sideroblasts in the BM or $>5\%$ with SF3B1 mutation.</p> <p>Presence of megakaryocytic atypia resembling ET or MF.</p>

MDS/MPN unclassifiable	Myeloid neoplasm with mixed MDS and MPN features, not meeting WHO criteria for other MDS/MPN overlap neoplasms, MDS or MPN.
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Table 1, WHO 2016 diagnostic criteria for Combined myelodysplastic syndrome/myeloproliferative neoplasm subclassification.

Select the subclassification that is appropriate for the MDS/MPN and check the box next to it.

3.1. CMML type

The prototype and most common MDS/MPN is chronic myelomonocytic leukaemia (CMML), which is characterized 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: **Myelodysplastic** (MD-CMML, WBC < 13x10⁹/L) and **Myeloproliferative** (MP-CMML, WBC > 13x10⁹/L). 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.

3.2. CMML WHO subclassification (2016)

According to the WHO (1), CMML can be further subclassified according to the percentage of blasts in peripheral blood and in bone marrow into CMML-0, CMML-1 and CMML-2:

CMML WHO subclassification	Description
CMML-0	<2% blasts in the blood and <5% blasts in the bone marrow
CMML-1	2-4% blasts in the blood and/or 5-9% blasts in the bone marrow

¹ Germline mutations (indicative of Noonan syndrome) need to be excluded.

CMML-2	5-19% blasts in the blood and 10-19% blasts in the bone marrow or presence of auer rods
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Table 2, WHO 2016 subclassification for CMML.

If the exact CMML subclassification is unknown, select **Unknown**.

4. Therapy-related MDS/MPN

Indicate if MDS/MPN developed in response to medical treatment (therapeutic agents or radiation). If the diagnosis of MDS/MPN is therapy-related, answer **Yes**. Otherwise, check **No**. If it is unknown whether or not the diagnosis of MDS/MPN was therapy-related, check **Unknown**.

Chromosome analysis

5. Chromosome analysis done before treatment

(all methods including FISH):

In this section describe the results of all chromosome analyses (performed at/after diagnosis but before the treatment).

Not done or failed - the chromosome analysis has not been done or failed;

Yes, abnormal results - the chromosome analysis has been performed and at least one of the results has been found to be abnormal. In addition, indicate the total number of different abnormalities present in all analyses with abnormal results (number of abnormalities present).

Yes, normal results - the chromosome analysis has been performed and all the results have been found normal;

Unknown - it is unknown whether the chromosome analysis has been done or not.

5.1. Date of chromosome analysis (if tested)

Indicate the date of the chromosome analysis. If the results were normal, add the date of the first test with normal results.

5.2. Chromosome analysis details

See the cytogenetics form or ask the cytogenetics team and consult your physician.

If chromosome analysis was performed, indicate for each abnormality in the table whether it was **Absent** or **Present**. If cytogenetics were not evaluated, report **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**.

5.3. Transcribe the complete karyotype

if it is not possible to report the chromosome analysis results as per abnormalities table.

Preferably the table above with abnormalities should be completed. If the result of the chromosome analysis is too complex, the complete karyotype should be described here.

Describe all abnormalities according to the ISCN karyotype nomenclature. This notation includes the total number of chromosomes, the sex chromosomes, and any extra or missing 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

6. Molecular markers analysis done before treatment

Indicate if molecular marker analysis was done or not before the treatment. Check **Unknown** if it is not known whether it was performed.

6.1. Date of molecular marker analysis (if tested)

Indicate the date of the molecular marker analysis.

6.2. Molecular marker analysis details

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

Bibliography

1. Campo E, Harris NL, Pileri SA, Jaffe ES, Stein H, Thiele J. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. IARC Who Classification of Tum; 2017. 586 p.