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GUIDELINE

BSH Guidelines

Diagnosis and evaluation of prognosis of myelofibrosis: A British Society for Haematology Guideline

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SUMMARY AND AIMS

This document represents an update of the British Society for Haematology (BSH) guideline on myelofibrosis (MF) first published in 2012 and updated in 2015.[1] This guideline aims to provide healthcare professionals with clear guidance on the diagnosis and prognostic evaluation of primary myelofibrosis (PMF), as well as post-polycythaemia vera myelofibrosis (post-PV MF) and post-essential thrombocythaemia myelofibrosis (post-ET MF). A section on prefibrotic MF is also included. A separate BSH Guideline covers the management of MF and is published alongside this guideline.

METHODOLOGY

These guidelines were compiled according to the BSH process https://b-s-h.org.uk/media/16732/bsh-guidance-development-process-dec-5-18.pdf. The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria can be found at http://www.gradeworkinggroup.org. Recommendations are based on a review of the relevant MF-related literature using Medline, PubMed/Medline and Cochrane searches beginning from 2012 up to mid-2022. Filters were applied to include only publications written in English, studies carried out in humans, clinical conferences, congresses, clinical trials, clinical studies, meta-analyses, multicentre studies and randomised controlled trials. Exclusion criteria included papers published in non-English journals and those publications without an abstract.

REVIEW OF THE MANUSCRIPT

Review of the manuscript was performed by the BSH Guidelines Committee Haemato-oncology Task Force, the BSH Guidelines Committee and the Haemato-oncology sounding board of the BSH. We invited two global expert external reviewers to review contents—Professor Ruben Mesa and Professor Alessandro Vannucchi. This guideline has also been reviewed by patient representatives from MPN Voice.

INTRODUCTION

Myelofibrosis encompasses PMF, post-ET MF and post-PV MF. It is characterised by clonal haematopoietic stem cell proliferation and elevated levels of pro-inflammatory

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cytokines, resulting in reticulin deposition and collagen fibrosis. The annual incidence is estimated at 1–2 individuals per 100 000 of the population in the United Kingdom, with an equal sex incidence.[2] All patients newly diagnosed with MF should be reported to the National Cancer Registry, via the multidisciplinary meeting, and to MF-specific registries if available.

CLINICAL FEATURES

Clinical features of MF are heterogeneous and may include anaemia, leucocytosis and extramedullary haemopoiesis, with progressive splenomegaly. Patients may experience constitutional symptoms, consequences of progressive splenomegaly (pain, early satiety, portal hypertension and dyspnoea), progressive marrow failure and have an inherent risk of leukaemic transformation.

Palpable splenomegaly is present in up to 80% of patients. Clinical palpation is the easiest method to evaluate spleen size, with the patient in the supine position. Ideally, a simple measuring tape can be used to record the size of an enlarged spleen below the left costal margin in centimetres (cm). Ultrasound may aid spleen size determination in a more uniform manner. In MF trials, the International Working Group-Myeloproliferative Neoplasm Research and Treatment (IWG-MRT) criteria utilised spleen volume as part of the clinical improvement response; this can be derived from computed tomography or magnetic resonance imaging. This is not a requirement in routine clinical practice.

Myelofibrosis frequently has a significant symptom burden that can negatively impact on quality of life, activities of daily living and functional status. Validated tools that have been developed to objectively measure symptom burden include the MF Symptom Assessment Form (MF SAF), MPN Symptom Assessment Form (MPN SAF) and MPN-SAF Total Symptom Score (MPN-SAF TSS—MPN 10).[3,4] The MPN-SAF TSS is an abbreviated symptom assessment tool that measures 10 symptoms through patient self-assessment on a linear scale from 0 (absent) to 10 (worst imaginable), namely: fatigue, early satiety, abdominal discomfort, inactivity, concentration problems, night sweats, pruritus, bone pain, fever and weight loss. Regular use of MPN-SAF TSS provides an indication of symptom status and treatment response and should be performed at each clinical review as appropriate.

Thrombosis risk is often underestimated in MF, in particular for those in the so-called lower prognostic groups with a *JAK2* V617F mutation.[5] An individualised risk assessment is warranted.

Finally, it is well established that some MF patients are at risk of non-cirrhotic portal hypertension, in particular those with bulky splenomegaly.[6] Where clinical signs (e.g. the presence of ascites, anterior abdominal wall dilated veins or signs associated with liver impairment) or liver imaging/transient elastography suggest the presence of portal hypertension, consideration should be given, in appropriate cases, for an oesophagogastroduodenoscopy (OGD) to be performed to rule out occult varices.

Recommendation

- **Spleen assessment by palpation, recorded as cm below the left costal margin, is the most straightforward method but may be limited by body habitus. Ultrasound aids spleen size determination in a more uniform manner, if required (Grade 1C).**
- **Assessment of symptoms using a validated tool, for example, the MPN-SAF TSS (MPN-10) is recommended at baseline, followed by dynamic assessment of symptom burden during follow-up (Grade 1B).**
- **An individualised risk assessment of thrombosis is warranted for all patients, in particular for those with the *JAK2* V617F mutation (Grade 1C).**
- **Where clinical signs or liver imaging/transient elastography suggest the presence of MF-related portal hypertension, consideration should be given for an oesophagogastroduodenoscopy (OGD) to be performed to rule out occult varices (Grade 2B).**

ESTABLISHING A DIAGNOSIS OF MF

Patients classically present with progressive anaemia, a leucoerythroblastic blood film with teardrop poikilocytes, splenomegaly and constitutional symptoms. These, along with pathogenic mutations (see below) and typical bone marrow (BM) morphological findings, form the basis of the diagnostic criteria proposed by both the World Health Organization (WHO) and the International Consensus Classification (ICC; Table 1).[7,8] Any patient being investigated for potential MPN with suspicious clinical features or atypical peripheral blood (PB) findings (cytopenia, left-shifted granulopoiesis, circulating blasts) should proceed to BM examination, which is essential for the diagnosis.[9]

A key morphological finding in the BM is a proliferation of atypical megakaryocytes,[7] showing clustering and abnormal localisation with hyperchromatic or bulbous nuclei, lying within an increased reticulin network with focal or diffuse collagen.[10] In advanced stages, osteosclerosis can be extensive. To establish a diagnosis and define the disease, reticulin grading is essential with a minimum of grade 2 (0–3 grading system).[11] Commercial reticulin staining kits detect only reticulin fibrosis necessitating additional staining for collagen (trichrome stain).[10–12] Separate scoring systems for collagen fibrosis and osteosclerosis have been recommended.[7,12] These may enable more accurate response assessment in patients receiving disease modifying therapies, although their clinical impact is yet to be established.[12,13] The BM should be reported in a Specialist Integrated Haematological Malignancy Diagnostic Service (SIHMDS) and as per either the WHO or ICC criteria. The classification used should be stated in the report and consideration should be given to stating the diagnosis according to both classifications.

TABLE 1 WHO diagnostic criteria for post-PV/ET myelofibrosis and overt PMF.

WHO 5th edition[7] ICC[8] 2022		WHO 5th edition ICC 2022	
Post-PV/ET MF		**Overt PMF**	
Major	Documentation of a previous established diagnosis of PV or ET	Major	Bone marrow biopsy showing megakaryocytic proliferation and atypia, accompanied by reticulin and/or collagen fibrosis grades 2 or 3
	Bone marrow fibrosis of Grade 2–3 on a 0–3 scale		*JAK2*, *CALR* or *MPL* mutation assessed by sensitive technique OR presence of another clonal marker (*ASXL1*, *EZH2*, *TET2*, *IDH1*, *IDH2*, *SRSF2* and *SF3B1*) OR absence of minor reactive bone marrow reticulin fibrosis
			Diagnostic criteria for *BCR*::*ABL1*-positive CML, PV, ET, MDS or other myeloid neoplasms not met[a]
Minor	Anaemia and a >20 g/L decrease from baseline haemoglobin concentration. A sustained loss of requirement of either phlebotomy (in the absence of cytoreductive therapy) or cytoreductive treatment for erythrocytosis	Minor	Anaemia not attributed to a comorbid condition
	Development of any two (or all three) of the following constitutional symptoms: >10% weight loss in 6 months, night sweats and unexplained fever (>37.5°C)		Leucocytosis $\geq 11 \times 10^9$/L
	Increased palpable splenomegaly >5 cm from the baseline or newly palpable		Splenomegaly detected clinically and/or by imaging
	Elevated LDH (for post-ET MF only)		Elevated LDH
	Leucoerythroblastosis		Leucoerythroblastosis
Diagnosis requires both major criteria and at least two minor criteria confirmed in two consecutive determinations		Diagnosis requires all three major criteria and at least one minor criterion confirmed in two consecutive determinations	

Abbreviations: ET, essential thrombocythaemia; ICC, International Consensus Classification; LDH, lactate dehydrogenase; MDS, myelodysplastic syndromes; MF, primary myelofibrosis; PMF, myelofibrosis; PV, polycythaemia vera; WHO, World Health Organization.

[a]Myeloproliferative neoplasms (MPN) can be associated with monocytosis or they can develop it during the course of the disease; these cases may mimic chronic myelomonocytic leukaemia (CMML); in these rare instances, a history of MPN excludes CMML, whereas the presence of MPN features in the bone marrow and/or MPN-associated mutations (in *JAK2*, *CALR* or *MPL*) tend to support the diagnosis of MPN with monocytosis rather than CMML.

It is essential to distinguish MF from other myeloid malignancies, and careful morphological assessment for features such as the degree of dysplasia is required.[14] In particular, it is important to highlight that systemic mastocytosis can be associated with significant marrow fibrosis. In patients with monocytosis, distinguishing between MF and chronic myelomonocytic leukaemia (CMML) can be challenging though genomic testing with targeted myeloid sequencing panels may help. This will not only detect mutations which are more specific to either disease but will also provide a *JAK2* mutant allele burden which is frequently reported to be higher in PMF than in CMML.[15,16]

Genetic tests for assessment of patients with MPN have been previously described.[17] Suspected PMF cases should be screened for common MPN driver mutations (affecting the *JAK2*, *CALR* and *MPL* genes), on either PB- or BM-derived DNA. Between 50% and 60% of PMF cases are positive for *JAK2* V617F, with the remaining 15%–35% and 6%–9% of cases testing positive for *CALR* exon 9 or *MPL* exon 10 mutations respectively.[17] Type 1/Type 1-like *CALR* mutations are much more prevalent in PMF than Type 2/Type 2-like mutations.[18]

Patients with BM histology and clinical features consistent with PMF or pre-PMF who test negative for *JAK2*, *CALR or MPL* mutations should be tested further using a myeloid gene panel and, ideally, karyotyping or genome-wide single nucleotide polymorphism (SNP) array.[17] Patients without a typical driver mutation in *JAK2*, *MPL* or *CALR* may be diagnosed as triple negative (TN) PMF, although this should prompt careful evaluation of the clinical picture and morphology to exclude the diagnosis of another myeloid neoplasm as highlighted above. In the absence of a clonal marker of disease, causes of secondary fibrosis also require exclusion (Table 2).[7,8,19] In addition, exclusion of *BCR*::*ABL1* is important for all TN patients with thrombocytosis and/or atypical features.

For patients with a confirmed diagnosis of PMF or post-PV/ET-MF, a myeloid panel and karyotyping/SNP array, performed on either PB or BM, provide important prognostic and potentially additional therapeutic target information and are generally recommended for allogeneic haematopoietic stem cell transplantation (allo-HSCT) candidates. In other patients, including those with pre-PMF, testing may be considered for prognostic purposes and/or whether additional genomic data will guide clinical management.

As a minimum, myeloid gene panels should include *ASXL1*, *CBL*, *CSF3R*, *DNMT3A*, *EZH2*, *KIT*, *KRAS*, *IDH1/2*, *NRAS*, *RUNX1*, *SETBP1*, *SF3B1*, *SH2B3*, *SRSF2*, *TET2*, *TP53* and *U2AF1*, together with full coding sequence coverage of

TABLE 2 Potential secondary causes of marrow fibrosis.

Causes of secondary bone marrow fibrosis	Examples
Infections	• HIV • Visceral leishmaniasis • Tuberculosis • Epstein–Barr virus infection
Autoimmune disorders	• Systemic lupus erythematosus • Sjögren syndrome • Anti-phospholipid syndrome • Juvenile idiopathic arthritis
Chronic inflammatory condition	
Hairy cell leukaemia	
Other haematological disorders	• Myelodysplastic syndromes • Hodgkin lymphoma • Chronic myeloid leukaemia • Some cases of acute myelomonocytic leukaemia • Paroxysmal nocturnal haemoglobinuria • Systemic mastocytosis • TAFRO (thrombocytopenia, anasarca, fever, reticulin fibrosis and organomegaly)
Metastatic malignancy	
Toxic chronic myelopathy	
Treatment with growth factors	• Recombinant human thrombopoietin agonists, for example, romiplostim • IL-11, for example, oprelvekin
Osseus or other metabolic disease	• Vitamin D deficiency • Hyperparathyroidism
Other causes may result in focal fibrosis	• Osteonecrosis/myelitis • Bone marrow irradiation • Previous trephine biopsy site • Grey platelet syndrome

JAK2, *MPL* and *CALR* exon 9. Broader mutation screens provide additional personalised prognostic information.[20–22] All cases should be discussed in a specialist multidisciplinary meeting. This should be a quorate meeting (e.g. clinical haematologists and representatives of the SIHMDS, etc.) as per national/local guidance on haemato-oncology multidisciplinary meetings.

Recommendations

- **All patients with suspected MF should undergo a diagnostic bone marrow biopsy and molecular testing for *JAK2*, *CALR* or *MPL* variants as appropriate (Grade 1A).**
- **The bone marrow trephine biopsy should have a reticulin stain and grade (Grade 1A) and consideration of trichrome staining. Ideally, the bone marrow should be reported in a SIHMDS and as per either the WHO or ICC criteria (Grade 2B).**
- **A myeloid gene panel, cytogenetic analysis and/or SNP array, and careful morphological examination is recommended for patients with bone marrow histology and clinical features consistent with PMF who test negative for *JAK2*, *CALR* and *MPL* (Grade 1B).**
- ***BCR*::*ABL1* should be excluded in cases with persistent thrombocytosis negative for *JAK2*, *CALR* and *MPL* variants, or those with atypical features (Grade 1B).**
- **Secondary causes of MF require exclusion in patients without typical MPN morphology or in those lacking an MPN-associated mutation (Grade 1A).**
- **Myeloid gene panel testing and conventional karyotyping and/or SNP array are recommended for all patients with PMF, post-PV or post-ET MF who are candidates for allogeneic stem cell transplant, or if it would be useful to guide patient management/prognostic assessment (Grade 1B).**
- **All diagnoses should be discussed in a specialist multidisciplinary meeting (Grade 1B).**

PROGNOSTIC EVALUATION IN PRIMARY AND POST-PV/POST-ET MF

Overall survival in MF varies widely and clinicians should be aware of the strengths and limitations of the many prognostic scores available to inform clinical use and guide discussions on therapy and management. These are summarised in Table 3, with suggestions where each score may be best utilised.

The International Prognostic Scoring System (IPSS) was the first risk stratification model to consider a large PMF cohort.[23] IPSS identified five factors associated with reduced patient survival: age >65 years, presence of constitutional symptoms (>10% weight loss in 6 months, night sweats, unexplained fever higher than 37.5°C), haemoglobin <100 g/L, white cell count $>25 \times 10^9$/L and ≥1% circulating blast cells. Use of the same five factors led to generation of the Dynamic IPSS (DIPSS) score, facilitating dynamic assessment during the disease course. This was further refined in the DIPSS-plus risk stratification by three additional risk factors (unfavourable karyotype, thrombocytopenia (platelets $<100 \times 10^9$/L) and red cell transfusion dependence).[24,25]

Approximately 40% of patients with PMF have an abnormal karyotype.[25,29–31] Patients with inv(3), −5/5q, −7/7q−, +8, 11q23 and 12p−, i(17q), or complex karyotypes (>2 abnormalities) have significantly poorer outcomes.[29,31–33] *JAK2* V617F and *MPL* mutations have been associated with a worse prognosis compared to *CALR* mutations in several studies. Prognostic advantage of a *CALR* mutation may, however, only be confined to Type 1 or Type 1-like mutations.[18,34–36] Overall survival for patients with TN MF appears worse than for those patients with a *JAK2*- or *MPL*-mutation.[34,36] So-called 'high molecular risk' (HMR) pathogenic mutations in five genes (*ASXL1*, *SRSF2*, *EZH2*, *IDH1* and *IDH2*) have been shown to adversely impact life expectancy and increase the likelihood of leukaemic transformation in MF.[37] Patients with >1 HMR mutation have a particularly poor prognosis. Mutations in *TP53*,

TABLE 3 Summary of prognostication models validated in patients with myelofibrosis.

Prognostic model	Patients (*n*)	When to use score	Type of patients included	Variables	Risk groups (median overall survival)
IPSS[23]	1054	Newly diagnosed PMF patients	Newly diagnosed PMF	Age >65 years (1) Hb <100 g/L (2) WBC >25 × 10^9/L (1) Circulating blasts ≥1% (1)	• Low (0) = 11.3 years • Intermediate-1 (1) = 7.9 years • Intermediate-2 (2) = 4 years • High (3–5) = 2.3 years
DIPSS[24]	525	PMF patients and can be applied at any stage in the disease course	Newly diagnosed PMF and follow-up	Age >65 years (1) Hb <100 g/L (2) WBC >25 × 10^9/L (1) Circulating blasts ≥1% (1) Constitutional symptoms (1)	• Low (0) = not reached • Intermediate-1 (1–2) = 14.2 years • Intermediate-2 (3–4) = 4 years • High (>4) = 1.5 years
DIPSS-PLUS[25]	793	PMF patients and can be applied at any stage in the disease course	Newly diagnosed PMF and follow-up	Age >65 years (1) Hb <100 g/L (2) WBC >25 × 10^9/L (1) Circulating blasts ≥1% (1) Constitutional symptoms (1) Unfavourable karyotype (1) Red cell transfusion need (1) Platelets <100 × 10^9/L (1)	• Low (0) = 15.4 years • Intermediate-1 (1–2) = 6.5 years • Intermediate-2 (3–4) = 2.9 years • High (>4) = 1.3 years
MIPSS 70 v 2.0[21]	406	PMF patients; validated up to the age of 70 years	Patients <70 years (*n* = 311) with PMF Included prefibrotic MF	VHR karyotype (4) Unfavourable karyotype (3) ≥2 HMR mutations (3) 1 HMR mutation (2) Type 1/like CALR absent (2) Hb <80 g/L females, Hb <90 g/L Male (2) Hb 80–99 g/L Females, Hb 90–109 g/L Male (1) Circulating blasts ≥2% (1) Constitutional symptoms (2)	• Very low (0) = not reached • Low (1, 2) = 16.4 years • Intermediate (3, 4) = 7.7 years • High (5–8) = 4.1 years • Very high (≥9) = 1.8 years
MYSEC-PM[26]	685	Patients with post-PV and post-ET MF	Post-PV and post-ET MF	Hb <110 g/L (2) Platelets <150 × 10^9/L (1) Circulating blasts ≥3% (2) *CALR* mutation absent (2) Constitutional symptoms (1) Age (0.15 per year of age)	• Low (<11) = not reached • Intermediate-1 (11–13) = 9.3 years • Intermediate-2 (14–16) = 4.4 years • High (>16) = 2.0 years
MTSS[27]	361	PMF or post-PV/ET MF planned for allogeneic stem cell transplantation	Patients presenting for first allogenic stem cell transplantation. 206 had primary myelofibrosis, 101 had post-ET or post-PV myelofibrosis	Age >57 years (1) WBC >25 × 10^9/L (1) Platelets <150 × 10^9/L (1) *ASXL1* mutated (1) Karnofsky Performance Status <90% (1) HLA-mismatched unrelated donor (2) Not *CALR*/*MPL* mutated	• Low (0–2) = 83% 5 years OS • Intermediate (3, 4) = 64% 5-year OS • High (5) = 37% 5-year OS • Very high (6–9) = 22% 5-year OS
Predict blood[22]	2035 MPN 309 MF Validation cohort (515 MPN, 190 MF)	PMF and post-PV/ET MF both at diagnosis and during disease course	At diagnosis or first referral	Multistate Cox proportional hazards algorithm incorporating 63 clinical and genomic variables to predict risk of survival and disease transformation to myelofibrosis and acute leukaemia	Individualised results for • Development of MF from ET/PV • Development of acute myeloid leukaemia from either chronic phase or any MF (either PMF or secondary MF) • Survival in ET/PV, PMF and secondary MF
RR6 model[28]	209 MF 40 MF in validation cohort	PMF and post-PV/ET MF patients, at least 6 months of therapy with RUX and may prompt therapy switch	PMF and post-ET/PV patients treated with ruxolitinib for at least 6 months	(1) RUX dose <20 mg twice daily at baseline, Months 3 and 6 (2) palpable spleen length reduction from baseline ≤30% at Months 3 and 6 (3) transfusion need at Months 3 and/or 6 (4) transfusion need at all time points (i.e. baseline and Months 3 and 6)	Response to RUX after 6 months (RR6), dissected three risk categories regarding OS • Low (median OS, not reached) • Intermediate (median OS, 61 months; 95% CI, 43–80) • High (median OS, 33 months; 95% CI, 21–50)

Abbreviations: CALR, calreticulin; ET, essential thrombocythaemia; Hb, haemoglobin concentration; HLA, human leucocyte antigen; HMR, high molecular risk; PMF, primary myelofibrosis; PV, polycythaemia vera; RBC, red blood cell; RUX, ruxolitinib; VHR, very high risk; WBC, white blood cell count.

TABLE 4 Diagnostic criteria for prefibrotic myelofibrosis as per WHO and ICC classification.

WHO 5th edition[7]		ICC 2022[8]	
Major	Megakaryocyte proliferation and atypia, without reticulin fibrosis grade >1, accompanied by increased age-adjusted bone marrow cellularity, granulocytic proliferation and (often) decreased erythropoiesis	Major	Bone marrow biopsy showing megakaryocytic proliferation and atypia, bone marrow fibrosis grade <2, increased age-adjusted BM cellularity, granulocytic proliferation and (often) decreased erythropoiesis
	Diagnostic criteria for *BCR::ABL1*-positive CML, PV, ET, MDS or other myeloid neoplasms not met		*JAK2*, *CALR* or *MPL* mutation or the presence of another clonal marker (assessed by cytogenetic analysis or sensitive NGS techniques, i.e. mutations associated with myeloid neoplasms)
	JAK2, *CALR* or *MPL* mutation OR presence of another clonal marker (i.e. mutations associated with other myeloid neoplasms) OR absence of minor reactive bone marrow reticulin fibrosis		Diagnostic criteria for *BCR::ABL1*-positive CML, PV, ET, MDS or other myeloid neoplasms not met
Minor	Anaemia not attributed to a comorbid condition	Minor	Anaemia not attributed to a comorbid condition
	Leucocytosis $\geq 11 \times 10^9$/L		Leucocytosis $\geq 11 \times 10^9$/L
	Splenomegaly detected clinically and/or by imaging		Palpable splenomegaly
	Elevated LDH		Elevated LDH
	Leucoerythroblastosis		
Diagnosis requires all three major criteria and at least one minor criterion confirmed in two consecutive determinations		Diagnosis requires all three major criteria and at least one minor criterion confirmed in two consecutive determinations	

Abbreviations: BM, bone marrow; ET, essential thrombocythaemia; ICC, International Consensus Classification; LDH, lactate dehydrogenase; MDS, myelodysplastic syndromes; NGS, next-generation sequencing; PV, polycythaemia vera; WHO, World Health Organization.

U2AF1, *RUNX1*, *CBL*, *NRAS* and *KRAS* can also confer adverse outcomes.[20,22]

The mutation-enhanced IPSS (MIPSS70+ v2.0) score combines typical haematological features together with karyotype and mutations in 'HMR' genes and *U2AF1* Q157.[21] MIPSS70+ v2.0 (http://www.mipss70score.it/) takes into account varying severity of anaemia. The model included mainly patients <70 years with PMF and pre-PMF, and is more accurate than IPSS. Both DIPSS and MIPSS70+ v2.0 appear relevant to those patients eligible for transplant as the risk score correlates with post-transplant outcomes.[38,39] The so-called 'RR6 model' predicts survival in MF based on clinical response after 6 months of ruxolitinib (considers spleen length reduction, dose density of ruxolitinib and transfusion requirements; http://www.rr6.eu/).[28] For transplant-eligible patients, the clinical-molecular myelofibrosis transplant scoring system (MTSS) combines age, haematological and molecular parameters, patient fitness and degree of HLA matching to predict survival after allo-HSCT.[27] The MYSEC-PM score was developed specifically for patients with post-PV MF and post-ET MF.[26]

A personalised prognosis calculator for MPN patients (Predict blood; https://blood.predict.nhs.uk/) takes into account 63 patient demographic, clinical and molecular variables to predict personally tailored risk for both disease transformation and survival. The model incorporates many more variables than the risk scoring systems described above, does not dichotomise continuous risk variables (such as increasing age or worsening blood counts), and can predict several different disease outcomes simultaneously. It was shown to provide improved accuracy and greater discrimination over both DIPSS and IPSS, even when incomplete information on molecular variables was available.[22]

Prognostication can aid treatment decisions including allo-HSCT. No model can currently predict which patients may benefit from any particular therapy. In general, it is advisable to repeat dynamic prognostication for patients at regular intervals, for example annually, or particularly if there is clinical concern or change in disease phenotype.

Recommendations

- **All patients with MF should have a prognostic evaluation performed using one of the currently available validated scores (Grade 1B).**
- **Use of validated risk scores for prognostication can aid treatment decisions, including consideration for allo-HSCT (Grade 1B).**
- **Dynamic prognostic assessment should be performed appropriate to patient characteristics, particularly if there is a change in disease phenotype or loss of response to therapy (Grade 2C)**

FOCUS ON PREFIBROTIC MF

Diagnostic classification and prognostication

The diagnosis of pre-PMF and its distinction from other MPNs is also based on a combination of clinical, morphological and genomic features (Table 4).[7,8] It is important to

note that pre-PMF is entirely distinct from low-risk overt MF. Distinction of ET from pre-PMF often causes the most diagnostic difficulty. Compared to ET, patients with pre-PMF tend to have higher white cell and platelet counts, lower haemoglobin levels, higher lactate dehydrogenase and greater splenomegaly, and less favourable outcomes: reduced survival, increased leukaemic transformation and increased progression to overt MF.[40,41] Pre-PMF tends to have milder clinical features and better survival than overt PMF.[42,43]

There is recognised interobserver variability in distinguishing histological features of pre-PMF and ET,[44–48] albeit not fully consistent across studies.[49,50] This variability, together with the proportion of patients diagnosed as unclassifiable MPN[46,51] has led to the utility of the WHO criteria being questioned. Although the IPSET thrombosis score from ET has been validated for thrombotic risk in pre-PMF,[52] other conventional MF prognostic scores are not fully applicable. Novel prognostic modelling methods have been proposed for pre-PMF including mutational profiles.[53] A myeloid gene panel and cytogenetic evaluation is recommended at diagnosis in patients with pre-PMF who are considered to be future allo-HSCT candidates, or where more accurate prognostic information would aid management. Most patients are currently treated pragmatically according to clinical phenotype. There is a risk of thrombosis associated with pre-PMF which must be considered.

AUTHOR CONTRIBUTIONS

All authors contributed to guideline writing, review and editing.

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CONFLICT OF INTEREST STATEMENT

All authors have made a declaration of interests to the BSH and Task Force Chairs which may be viewed on request.

DISCLAIMER

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