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Evolution of WHO diagnostic criteria in "Classical Myeloproliferative Neoplasms" compared with the International Consensus Classification

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A lively discussion persists regarding the diagnostic criteria for essential thrombocythemia (ET), primary myelofibrosis (PMF) and polycythemia vera (PV), particularly in relation to early/pre-fibrotic myelofibrosis (pre-PMF), a disease entity initially introduced in 2001 by the 3rd edition of the World Health Organization (WHO) classification. The definition and criteria used to diagnose pre-PMF have been progressively modified over time. The most update definition of pre-PMF can be found in the International Consensus Classification (ICC) published in 2022. An updated largely similar definition is also incorporated in the recently published 5th edition of WHO classification (2024). Diagnostic criteria for ET have undergone changes up to 2016/17 for the revised 4th edition of the WHO. In particular the threshold value for platelets were lowered and the important discrimination between "true" and "false" ET (in reality pre-PMF) been widely acknowledged. To avoid misdiagnose in early phase PV, the criteria for gender-adjusted thresholds for hemoglobin/ hematocrit have been lowered and the identification of an appropriate bone marrow (BM) morphology was upgraded as a major diagnostic criterion. Given the prominent role of morphology in MPN-related diagnostic algorithms, the diagnostic adequacy of the BM biopsy (sample procurement and proper laboratory handling) as emphasized in former WHO editions and in the ICC, was not addressed by the WHO 5th. The essential role of genetic markers is recognized by both classifications. A comparison between the revised 4th edition WHO classification and the ICC versus the WHO 5th reveals no significant differences, with the exception of the occurrence of leukoerythroblastosis in pre-PMF considered by the latter as one of the minor diagnostic criteria which seems unwarranted. In contrast to the revised 4th edition, the majority of the microscopic images used for the WHO 5th due to their low magnification and poor technique, do not highlight the diagnosis differences among these entities.

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INTRODUCTION

Since 1995, the European Association for Haematopathology and the Society for Hematopathology have tried to introduce a new World Health Organization (WHO) classification of hematologic malignancies. Although focused on lymphoid neoplasms this classification included also myeloid, histiocytic, and mast cell neoplasms [1, 2]. A basic principle of the WHO system is that the classification of the hematopoietic neoplasms should not only utilize morphological findings, but also all available information as genetic profiles, immunophenotypes and well-documented clinical data [3].

Following the WHO classification, a lively discussion and even controversy still persist during the past 22 years [4–7]. This regards not only the "classical" major myeloproliferative neoplasms (MPNs) like essential thrombocythemia (ET), primary myelofibrosis (PMF) and polycythemia vera (PV) [8], but especially the existence of early/pre-fibrotic myelofibrosis (pre-PMF) [9–11]. Recently a group of international experts, including hematopathologists, oncologists, and geneticists met to update the revised 4th edition WHO classification system for hematopoietic tumors [6, 12, 13] and the new International Consensus Classification (ICC) was introduced in 2022 [14–16]. Concerning myeloproliferative neoplasms (MPNs), the classification confirmed a primary role for BM morphology in disease classification and diagnosis while also acknowledging the complementary impact of genetic markers [15]. It must be emphasized that the diagnosis of MPNs requires an integrated approach that includes hematologic and molecular genetic findings in addition to morphology. In relation to the latter, it cannot be underestimate how bone marrow (BM) biopsy interpretation remains the cornerstone of diagnosis [12, 13, 15, 17]. The concept has also been explicitly adopted by the 5th edition of the WHO in 2024 (essential and desirable diagnostic criteria) [7]. In this context it is important to note that the criteria of revised 4th edition WHO classification [6] and ICC [14] were applied by the 5th edition of the WHO in 2024 [7].

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HISTORICAL PRELUDE

The idea that PMF may be diagnosed even in the presence of a non-fibrotic BM and differentiated from ET and PV, first came in the late twentieth century [18]. The concept of a pre-fibrotic PMF was introduced by a group of pathologists and associated clinicians working together. It started around 1980 following evaluation of 1083 BM biopsies of MPN patients, including 454 cases (42%) with "neoplastic megakaryopoiesis" whose definition was based on the conspicuous atypia of the megakaryocytes as revealed by light microscopy, extending and confirming earlier ultrastructural findings [19]. In these patients BM features were described as chronic megakaryocytic-granulocytic myelosis (CMGM) because neutrophil granulopoiesis was regarded as neoplastic and both cell lineages revealed a complete difference compared to mature forms. At that time CMGM was separated from chronic granulocytic leukemia (CGL), which was only characterized by the presence of a single line proliferation. However, both entities were included in chronic myeloid leukemia (CML) because of the presence of the Philadelphia chromosome as subsequently demonstrated.

Primary or idiopathic thrombocythemia had to be differentiated from CMGM since there was no evidence for malignancy of the granulocytic series [20]. Altogether in the first reports, CMGM was considered to be merely a variant of CML. However, subsequently CMGM was separated from CML, and considered as an early phase of *BCR::ABL1* negative MPNs [21]. Already in 1984 more refined investigations of hematopoiesis in MPNs were performed by employing morphometric methods. The entities of MPNs studied included (i) chronic granulocytic leukemia (CGL/CML), (ii) agnogenic myeloid metaplasia in an early hypercellular stage (so-called CMGM), (iii) agnogenic myeloid metaplasia in an advanced fibrosclerotic stage or osteomyelofibrosis/sclerosis (MF/OMS), (iv) polycythemia vera (P. vera), and (v) primary (idiopathic, essential) thrombocythemia (PTH) [22]. For a consolidation of this classification mostly based on morphology, but especially for the so-called CMGM (Hannover Classification) [23–26] an integrated approach was warranted. By strictly following this strategy a close cooperation with clinicians based on retrospective analyses of an expanding and well-documented archive between 1988-1996 [27–32], the term and definition of CMGM disappeared. The concept of an early stage of PMF/pre-fibrotic PMF often mimicking ET was then introduced [33–35]. Alongside the integration of clinical and morphological data, it was largely accepted and included in the WHO classification in 2001 [3, 4].

The existence of a form of MPN as part of the spectrum of PMF and different from ET was a turning point but it sparked controversy and intense discussion for many years. Notwithstanding those arguments, pre-fibrotic PMF gained widespread acceptance which allowed its inclusion in the 2001 WHO Classification on MPNs [4]. Before 2001, the most frequently used criteria to diagnose ET and PV were that of the Polycythemia Vera Study Group (PVSG) founded already in 1967; pre-PMF was not known at that time [36]. After that a very important step was the molecular discovery of driver mutations specific for MPN [5, 37]. The presence of mutations plays a crucial role in establishing clonality, MPN subtype designation, and disease prognostication.

Coming to the most recent classifications such an integrated approach was used in the 4th edition of the WHO classification (2008) and for its revised 4th edition (2017). However, in contrast to previous WHO editions and the ICC [6, 12], a clinical advisory board was not used in preparation for the WHO 5th edition [7]. Both classifications emphasize a balanced integration of clinical, morphological, immunophenotypic, and genetic data [5–7, 12, 14, 15]. Regarding the diagnostic criteria of the revised 4th edition WHO classification [6, 12], the ICC [11–13], and the new 5th edition of the WHO [7] reveal no significant differences with the exception of the occurrence of leukoerythroblastosis in early/pre-PMF only included in the 5th WHO edition as one of the minor diagnostic criteria that seems to be unwarranted. Given the prominent role of morphology in MPN-related diagnostic algorithms, the diagnostic adequacy of the BM trephine biopsy (sample procurement and its laboratory handling) have been explicitly emphasized in former WHO editions and associated studies but were not discussed. Unfortunately, in contrast to the former WHO editions [4–6], the majority of figures in the WHO 5th edition, with their relatively low magnification and regrettably suboptimal technique, offer little support to a clear-cut morphologic diagnosis. Some difficulties would be expected in using the WHO 5th edition [7] due to the suboptimal quality of its illustrative BM morphology in contrast with the former WHO 4th edition [6, 12] and ICC [14–16] whose images provide adequate support to the diagnostic morphologic criteria.

Regarding ET following the updated PVSG criteria some amount of collagen fibers were allowed in the BM ("collagen fibrosis absent or < 1/3 biopsy area without marked splenomegaly and leukoerythroblastic reaction"), but no further specifications of the megakaryocytes or of other hematopoietic cell lineages [38, 39]. In ET patients a comparison between PVSG and WHO diagnostic criteria revealed significant differences regarding progression to myelofibrosis (MF), transformation to blast phase (BP) and loss of life expectancy/or survival [40]. At that time instead of PMF the name idiopathic myelofibrosis (IMF) was the preferred term [4, 5, 18, 27, 40–43] and fibrosis was graded with a semiquantitative system ranging from 0 (normal reticulin) to 3 (overt collagen) fibrosis [44]. The observed discrepancy in term of ET yielded the question whether cases of pre-PMF have been hidden within the PVSG-designated ET [38, 39], A thorough revision of a series of 839 *BCR::ABL1*-negative MPN patients revealed that out of 631 cases with a presumptive clinical diagnosis of ET only 483 (76.6%) fulfilled the PVSG diagnostic guidelines and the remaining cohort was unclassifiable, while the remaining 208 patients presented either pre-fibrotic IMF, overt IMF or PV [40]. WHO-defined or "true" ET included only 162 patients, while pre-fibrotic-IMF accounted for 321 cases, i.e. almost double the incidence. Few years later similar frequencies were calculated (476 PVSG-confirmed ET patients compared to167 WHO "true" ET cases plus 309 patients with pre-fibrotic, early IMF) [43].

The high percentage of pre-fibrotic-IMF may reflect a bias since these cases were reviewed by a reference center for BM pathology. Other groups have indeed found significantly lower proportions of pre-fibrotic, early IMF [41, 42, 45].

A weak point of the PVSG criteria [38, 39] is their failure at discriminating between collagen and reticulin fibers and the lack of a complete morphologic hematopoietic lineages assessment, and particularly the non-inclusion of megakaryocyte morphology. Since 2008 the term IMF was changed to primary myelofibrosis (PMF) [5, 6, 27] and fiber grades 0 and 1 called pre-fibrotic/ early PMF and fiber-grades 2 and 3 advanced / overt PMF [44, 46].

After its introduction as an entity, pre-PMF has caused controversies centered on the poor reproducibility of BM histological features used to distinguish ET from pre-PMF [47]. To improve this unwanted situation a key step was the creation by J.W. Vardiman and A. Tefferi of a Clinical Advisory Committees (CAC) [37, 48] that included a cadre of very active and expert international hematopathologists and oncologists participating in a number of sessions and subsequent consultations. In addition, several combined sessions of clinicians and pathologists chaired by T. Barbui reanalyzed 1104 multicenter patients with a local diagnosis of ET and the discrimination between true versus false ET (pre-PMF) [49].

An overall consensus of 82% (2033 patients) was reported by a blinded evaluation of five groups [47, 49–52] contrasting an only 63% concordance obtained in a smaller cohort of 655 cases [53–56]. However, it appears that the latter study did not meet pre-requirement steps necessary to ensure accurate results including prior experience in applying the diagnostic criteria and

Table 1. Essential Thrombocythemia (ET) starting with a high threshold level of sustained platelet count (WHO refs. # [4–7] versus ICC ref.# [14]).

Year Major criteria	2001 Jaffe ES et al. ref. # [4]	2008 Swerdlow SH et al. ref. # [5]	2017 Swerdlow SH et al. ref. # [6]	2024 Akkari Y et al. ref.# [7]	2022 Arber DA. et al. ref. # [14]
Platelet count	≥ 600 x10^9/L	≥ 450 x10^9/L	≥ 450 x10^9/L	≥ 450 x10^9/L	≥ 450 x10^9/L
Bone marrow morphology	Bone marrow biopsy specimen showing proliferation mainly of the megakaryocytic lineage with increased numbers of enlarged, mature megakaryocytes	Bone marrow biopsy specimen showing proliferation mainly of the megakaryocytic lineage with increased numbers of enlarged, mature megakaryocytes. No significant increase or left-shift of neutrophilic granulopoiesis or erythropoiesis	Bone marrow biopsy showing proliferation mainly of the megakaryocytic lineage, with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei; no significant increase or left shift in neutrophilic granulopoiesis or erythropoiesis; very rarely a minor (grade 1) increase in reticulin fibers	Bone marrow biopsy showing proliferation mainly of the megakaryocytic lineage, with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei; no significant increase or left shift in neutrophilic granulopoiesis or erythropoiesis; very rarely a minor (grade 1) increase in reticulin fibers	Bone marrow biopsy showing proliferation mainly of the megakaryocytic lineage, with increased numbers of enlarged, mature megakaryocytes with hyperlobulated staghorn-like nuclei, infrequently dense clusters; no significant increase or left shift in neutrophil granulopoiesis or erythropoiesis; no relevant BM fibrosis
Criteria of Exclusion	No evidence of PV, CML, PMF, MDS; no evidence for reactive thrombocytosis	Not meeting WHO criteria for PV, PMF, *BCR::ABL1* positive CML, MDS or other myeloid neoplasm	WHO criteria for *BCR::ABL1* positive chronic myeloid leukemia, polycythemia vera, primary myelofibrosis or other myeloid neoplasms are not met	WHO criteria for *BCR::ABL1* positive chronic myeloid leukemia, polycythemia vera, primary myelofibrosis or other myeloid neoplasms are not met	Diagnostic criteria for *BCR::ABL1* positive CML, PV, PMF, or other myeloid neoplasms are not met
Clonal genetic abnormality		Demonstration of *JAK2* V617F or other clonal marker, or in the absence of *JAK2* V617F, no evidence for reactive thrombocytosis	*JAK2*, *CALR*, or *MPL* mutation	*JAK2*, *CALR*, or *MPL* mutation	*JAK2*, *CALR*, or *MPL* mutation
Minor Criteria			Presence of a clonal marker or absence of evidence of reactive thrombocytosis	1. Presence of a clonal marker or 2. Exclusion of reactive thrombocytosis	Presence of a clonal marker or absence of evidence of reactive thrombocytosis
	Diagnosis requires meeting criteria 1 and 2 and criteria of exclusion	Diagnosis requires meeting all four criteria	The diagnosis of essential thrombocythemia requires that either all major criteria or the first 3 major criteria plus the minor criterion are met	The diagnosis of essential thrombocythemia requires that either all major criteria or the first 3 major criteria plus the minor criterion are met	The diagnosis of ET requires either all major criteria or the first 3 major criteria plus the minor criteria

WHO World Health Organization, *ICC* International Consensus Classification, *CML* chronic myeloid leukemia, *PV* polycythemia Vera, *ET* Essential Thrombocythemia, *PMF* primary myelofibrosis, *MDS* Myelodysplastic Syndromes.

following specific sample procurement and processing guideline as outlined in the post-2001 WHO classification fascicles [5, 6, 37] as well as described in the current ICC system [14–16].

From these data it appears that reproducibility still remains a challenge, particularly in the context of collaborative clinical studies involving patients diagnosed in different laboratories leading to inconsistent information. Adding to the morphological evaluation an adequate number of support data (e.g. biomarker results and other laboratory parameters) may be of help in decreasing classification uncertainty.

In term of specimen procurement-related guidelines, BM smears and trephine biopsies must be done at time of diagnosis, or within a very short time thereafter, and in the absence of active therapy, particularly cytoreductive drugs. Moreover, BM biopsy cores should be ≥ 1.5 cm in length, artefact-free and performed at right angle to the cortical bone, and accompanied by aspirates and smears that are properly obtained and processed [5, 6, 15]. Unfortunately, the diagnostic impact and relative incidence of discriminating morphological features according to well-standardized morphological criteria as outlined in former WHO editions and the ICC together with the necessary pre-requirements for proper handling of the BM specimens [15], were not adopted by the 5th edition of the WHO [7].

Current classification guidelines also recommend that peripheral blood and BM specimens be processed for cytogenetic and molecular studies, and the latter must include screening for *JAK2* (both exons 12 and 14), *CALR* and *MPL* mutations [15]. A carefully processed specimen should allow accurate grading of fibrosis (3-grade scoring system) including differentiation between reticulin versus collagen [44, 46]. In particular, the presence of collagen deposition represents the *sine qua non* of fibrotic stage PMF as well as of Post PV/ET myelofibrosis. Its presence makes untenable a diagnosis of "chronic phase" ET. Assessment of age-adjusted hematopoietic cellularity, distribution /organization of the different hematopoietic cell lineages and their relative proportion, and identification of key morphologic hallmarks, generates unique histological patterns of significant diagnostic value [6, 57].

ESSENTIAL THROMBOCYTHEMIA (ET)

Concerning the evolution of WHO diagnostic criteria in ET over the years as shown in Table 1 most changes occurred in 2016/17 with the revised 4th edition. These included a lower threshold value for thrombocytosis, the addition of more detailed BM findings, and better clarification of the role of mutations [5, 6, 12, 13]. Of note, both the ICC [14–16] and the 5th WHO edition [7] adopted these criteria without relevant changes. Regarding clinical data at diagnosis and follow-up two large studies, an older one with 891 ET patients [34] and a recent one with 1,000 cases [58, 59] are informative. The higher platelet count (≥ 600 x10^9/L) proposed by the 2001 WHO classification [4]. was found to be inadequate for capturing ET patients with a much lower platelet count at diagnosis, but presenting with relevant thromboembolic or thrombotic findings [48, 60–62]. After extensive discussion and clinical validation, finally a threshold of 450 ×10^9/L was adopted as a WHO criterion being more adjusted to gender and race [63–66]. Driver mutation (i.e. *JAK2*/*CALR*/*MPL*) distribution in ET [14, 15, 49] is somewhat similar to that seen in pre-PMF or overtly fibrotic PMF, with the exception that frequency of *MPL* mutation is higher in PMF and triple-negative mutation status ET (*JAK2* V617F 50-70%, *CALR* 20-25%, *MPL* 3%-8%, and triple-negative 10 -25%) [58, 66–68].

Functional consequences of different types of driver mutations have been studied [69]. The presence of *MPL* mutation in patients with ET is associated with increased risk of myelofibrotic progression [70, 71].

In term of *CALR* mutations, patients carrying type 1/1-like mutation have a significant higher risk of myelofibrotic progression than those carrying type 2/2-like *CALR* mutation [70, 72].

The effects in patients of different mutation subtypes parallel findings reported in conditional inducible knock-in mice expressing chimeric murine CALR del52 or ins5 [73].

Prognostic relevance for karyotype is well established [74]. Next generation sequencing (NGS) revealed 53% of 183 patients with WHO-confirmed ET to harbor one or more sequence variants/mutations other than *JAK2* V617F/*CALR*/*MPL*; the most frequent were *TET2* and *ASXL1* [75].

Prognostic significance was demonstrated by multivariable analysis that included IPSET (international prognostic score for ET) variables. This revealed that abnormal karyotype, age >60 years, leukocytosis >11 × 10^9/L, and male gender were independently associated with inferior survival; abnormal karyotype and age >60 years remained significant, along with *SF3B1*/*SRSF2*/*U2AF1*/*TP53* mutations, when the latter was included in the multivariable model [74].

It is remarkable that different groups have reported that in strictly WHO-confirmed ET a significant preponderance of female patients may be observed according to the Female/Male (F/M) quotient: in three studies including 2388 patients with ET and pre-PMF the relevant F/M quotients of 865/588 versus 520/415 were found, respectively [47, 49, 76]. (Concerning the 1000 ET study, although partially overlapping with the cohorts of the Mayo Clinic 63% and of the Florence cohort 65% of the patients were female [58, 59]. Contrasting pre-PMF with relatively little differences in a large cohort of 4079 WHO-confirmed ET the F/M quotient reached 24536 versus 1543 [77–80]. No significant differences were detectable for F/M quotients in 660 pre-PMF cases with 317/343 proportions [81, 82]. Concerning PV the 3315 patients revealed no difference between the genders by showing a F/M quotient of 1661 /1654 [78, 80, 83]. Regarding large series of presumptive ET cases a missing predominance of females may indicate "false" ET (pre-PMF) or initial (latent) PV [84, 85]. This probability of the female gender in prior WHO and ICC-defined ET [16] has not been described in the 5th edition of the WHO in which no gender data were provided [7]. The diagnostic advantage of this phenomenon is that in large series of presumptive ET a missing predominance of females may indicate" false" ET diagnostic attribution, i.e., cases were in reality pre-PMF but misdiagnosed as ET or represented initial (latent) PV [84, 85]. Unfortunately, as we said before, this predominance of female gender in prior WHO and ICC-defined ET is lacking in the 5th edition of the WHO perhaps due to the absence in the latter of a CAC component [7].

POLYCYTHEMIA VERA (PV)

The current diagnostic parameters for PV include the presence of a *JAK2* mutation in association with hemoglobin (Hb) / hematocrit (Hct) levels of >16.5 g/dL/49% in men or 16 g/dL/48% in women; morphologic confirmation by BM examination is a requirement for most patients but not mandated in all instances [86]. As shown in Table 2, in early classifications an elevated red blood cell (RBC) mass >25% above mean normal predicted value and higher values of Hb >18.5 g/dL in men; >16.5 g/dL in women were the major diagnostic parameters. Those also include a rarely performed in vitro test, endogenous erythroid colony formation (EEC). BM morphology was only included as a minor diagnostic criterion. According to a large study on 1545 patients using the WHO 4th edition (2008) - confirmed PV patients an increased RBC mass was found in 91% and EEC in only 73% of cases [83]. Similar values of increased RBC mass (94%) were reported in all 290 PV patients of another cohort [86]. Application of the EEC assay as a minor diagnostic criterion was discarded since the 2016 revised 4th edition of the WHO due to limited practicability (time consuming, costly) [6, 12]. Most important is that this test was never standardized for clinical use, and it is usually only available in specialized research laboratories [17, 86, 87]. Serum erythropoietin levels below the reference range [88] was an additional minor

Table 2. Polycythemia vera and the lowering of its hemoglobin/hematocrit thresholds.

Year Major criteria	2001 Jaffe ES et al. ref. # [4]	2008 Swerdlow SH et al. ref. # [5]	2017 Swerdlow SH et al. ref. # [6]	2024 Akkari Y et al. ref. # [7]	2022 Arber DA. et al. ref. # [11]
Blood	A1 Elevated RBC mass >25% above mean normal predicted value or Hb >18.5 g/dL in men; >16.5 g/dL in women A2 No cause of secondary erythrocytosis A3 Splenomegaly A4 Clonal genetic abnormality other than Ph chromosome or *BCR/ABL* fusion gene A5 Endogeneous erythroid colony formation in vitro B1 Thrombocytosis >400 x10^9/L B2 WBC > 12 ×10^9/L B4 Low serum erythropoietin levels	Hemoglobin >18.5 g/dL in men, >16.5 g/dL in women or other evidence of increased red cell volume	Elevated hemoglobin concentration (> 16.5 g/dL in men; >16.0 g/dL in women or elevated hematocrit (> 49% in men and 48% in women) or increased red blood cell mass (> 25% above mean normal predicted value)	Elevated hemoglobin concentration (> 16.5 g/dL in men; > 16.0 g/dL in women) or elevated hematocrit (> 49% in men; >48% in women)	Elevated hemoglobin concentration or elevated hematocrit or increased red blood cell mass: hemoglobin: >16.5 g/dL in men and > 16.0 g/dL in women; hematocrit: >49% in men and >48% in women; red blood cell mass: >25% above mean normal predicted value
Bone marrow morphology	B3 Bone marrow biopsy showing panmyelosis with prominent erythroid and megakaryocytic proliferation	Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid, granulocytic, and megakaryocytic proliferation	Bone marrow biopsy showing age-adjusted hypercellularity with trilineage growth (panmyelosis), including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic (differences in size) mature megakaryocytes	Bone marrow biopsy showing age-adjusted hypercellularity with trilineage growth (panmyelosis), including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic (differences in size) mature megakaryocytes	Bone marrow biopsy showing age-adjusted hypercellularity with trilineage proliferation (panmyelosis), including prominent erythroid, granulocytic, and increase in pleomorphic, mature megakaryocytes without atypia
Clonal genetic abnormality		Presence of *JAK2* V617F or other functionally similar mutation such as *JAK2* exon 12 mutation	Presence of *JAK2* V617F or *JAK2* exon 12 mutation	Presence of *JAK2* V617F or *JAK2* exon 12 mutation	Presence of *JAK2* V617F or *JAK2* exon 12 mutation
Minor Criteria		Serum erythropoietin level below the reference range for normal endogenous erythroid colony formation in vitro	Subnormal serum erythropoeitin level	Subnormal serum erythropoeitin level	Subnormal serum erythropoietin level
	Diagnosis of PV when A1 + A2 and any other category A are present, or when A1 + A2 and any two of category B are present	Diagnostic criteria for polycythemia vera (PV). Diagnosis requires the presence of both major criteria and one minor criterion or the presence of the first major criterion together with two minor criteria	The diagnosis of polycythemia vera requires either all major criteria or the first 3 major criteria plus the minor criterion	The diagnosis of polycythemia vera requires either all major criteria or the first 3 major criteria plus the minor criterion	The diagnosis of PV requires either all 3 major criteria or the first 2 major criteria plus the minor criterion

(WHO refs. # [4–7] versus ICC ref. # [14]).
PV, polycythemia Vera.

Table 3. Pre-fibrotic /early primary myelofibrosis (Pre-PMF) (WHO refs. # [4–7] versus ICC ref. # [14]).

Year Major criteria	2001 Jaffe ES et al. ref. # [4]	2008 Swerdlow SH et al. ref. # [5]	2017 Swerdlow SH et al. ref. # [6]	2024 Akkari Y et al. ref.# [7]	2022 Arber DA. et al. ref. # [14]
Blood	No or mild leukoerythroblastosis, no or minimal red blood cell poikilocytosis, few if any dacrocytes				
Bone marrow morphology	Hypercellularity, Neutrophilic proliferation, Megakaryocytic proliferation and atypia (clustering of megakaryocytes, abnormally lobulated megakaryocytic nuclei, naked megakaryocytic nuclei). Minimal or absent reticulin fibrosis	Presence of megakaryocytic proliferation and atypia in the absence of significant reticulin fibrosis accompanied by an increased bone marrow cellularity characterized by granulocytic proliferation and often decreased erythropoiesis (i.e., pre-fibrotic cellular phase of disease)	Megakaryocytic proliferation and atypia, without reticulin fibrosis grade >1 accompanied by increased age-adjusted bone marrow cellularity, granulocytic proliferation, and (often) decreased erythropoiesis	Megakaryocytic proliferation and atypia, without reticulin fibrosis grade >|1, accompanied by increased age-adjusted bone marrow cellularity, granulocytic proliferation, and (often) decreased erythropoiesis	Bone marrow biopsy showing megakaryocytic proliferation and atypia, bone marrow fibrosis grade<2, increased age-adjusted BM cellularity, granulocytic proliferation, and (often) decreased erythropoiesis
Criteria of Exclusion		Not meeting WHO criteria for polycythemia vera, *BCR::ABL1* positive chronic myeloid leukemia, myelodysplastic syndromes or other myeloid neoplasms	WHO criteria for polycythemia vera, *BCR::ABL1* positive chronic myeloid leukemia, myelodysplastic syndromes or other myeloid neoplasms are not met	WHO criteria for *BCR* :: *ABL1*–positive chronic myeloid leukemia, polycythemia vera,essential thrombocythemia, myelodysplastic syndromes, or other myeloid neoplasms are not met	Diagnostic criteria for *BCR::ABL1* positive CML, PV, ET, myelodysplastic syndromes, or other myeloid neoplasms are not met
Clonal genetic abnormality		Demonstration of *JAK2* V617F or other clonal marker (e.g. *MPL* W515K/L), or in the absence of a clonal marker, no evidence that the bone marrow fibrosis or other changes are secondary to infection, autoimmune disorder or other chronic inflammatory condition, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies	*JAK2*, *CALR*, or MPL mutation or presence of another clonal marker or absence of minor reactive bone marrow reticulin fibrosis	*JAK2*, *CALR*, or *MPL* mutation or presence of another clonal marker or absence of minor reactive bone marrow reticulin fibrosis	*JAK2*, *CALR*, or *MP*L mutation or presence of another clonal marker or absence of reactive bone marrow reticulin fibrosis
Minor Criteria	Hematologic parameters variable but often: mild anemia, mild to moderate leukocytosis, mild to marked thrombocytosis, no or mild splenomegaly or hepatomegaly	Leukoerythroblastosis Increase in serum lactate dehydrogenase level Anemia Splenomegaly (degree of abnormality may be borderline)	Presence of at least one of the following, confirmed in 2 consecutive determinations: Anemia not attributed to comorbid condition Leukocytosis ≥ 11 × 10 ^{9}/L Palpable splenomegaly Serum lactate dehydrogenase level above the upper limit of the institutional reference range	Presence of at least one of the following, confirmed in 2 consecutive determinations: Anemia not attributed to comorbid condition: Leukocytosis ≥ 11 × 109/ L; Splenomegaly detected clinically and/or by imaging; Lactate serum dehydrogenase level above the upper limit of the institutional reference range; Leukoerythroblastosis	Anemia not attributed to a comorbid condition Leukocytosis ≥ 11×10^{9}/L Palpable splenomegaly Lactate serum dehydrogenase level above the reference range
	Diagnosis requires meeting criteria 1 and 2 and criteria of exclusion	Diagnosis requires meeting all 3 major and 2 minor criteria	The diagnosis of pre-fibrotic/ early primary myelofibrosis requires that all 3 major and at least 1 minor criterion are met	The diagnosis of pre-fibrotic primary myelofibrosis requires that all 3 major criteria and at least 1 minor criterion are met.	The diagnosis of pre-PMF requires all 3 major criteria and at least 1 minor criterion confirmed in 2 consecutive determinations

WHO World Health Organization, *ICC* International Consensus Classification, *CML* chronic myeloid leukemia, *PV* polycythemia Vera, *ET* Essential Thrombocythemia, PMF Primary Myelofibrosis.

criterion used in all WHO classifications [78, 83, 89, 90] and is still present in both the ICC and WHO 5th edition [4–7, 14–16] As has been previously mentioned, the diagnostic criteria for PV had been significantly modified in the revised 4th edition WHO classification [6, 12, 13, 91] with the inclusion of BM morphologic characteristics as one of the three major diagnostic criteria [65, 92, 93]. This allowed lowering of the Hb/Hct thresholds for diagnosis (16.5 g/dl/49% in men and 16 g/dl/48% in women). (Table 2) A comparison between the ICC parameters [14–16] and the 5th edition of the WHO criteria [7] reveals an almost complete consensus with the exception of the usage of RBC mass testing for differentiating between true polyglobulia and pseudopolyglobulia which was considered by the WHO unsuitable to routine clinical settings and therefore eliminated.

Evaluation of WHO criteria require close cooperation between hematopathologist and clinician [94, 95], especially the discrimination between so-called initial or pre-polycythemic (latent or masked) PV (mPV) versus ET may be challenging [84, 85, 96]. Molecular profiles that include *JAK2* V617F or *JAK2* exon 12 mutation / *CALR*, in addition to *JAK2* and *MPL* are considered to confirm clonality and specific diagnosis [17, 66, 75, 97, 98].

In the years 2014 /15 the term mPV was re-introduced [99, 100] to identify *JAK2*-mutated ET patients presenting with a latent/initial (pre-polycythemic, prodromal) manifestation, BM morphology consistent with PV and display raised Hb levels (16.0 and 18.5 g/dl for men and 15.0 and 16.5 g/dl for women). Later in accordance with the British Committee for Standards in Haematology (BCSH) guidelines criteria [101] a Hct level of 49% in men and 48% in women was considered as the cutoff threshold value [102] for discrimination *JAK2*-mutated ET from mPV [103]. It is evident that the clinical utility of using Hct as reference variable is supported also by results of clinical trials which explicitly recommend to use the Hct threshold for monitoring treatment [86]. Regarding clinical findings and relationship to overt PV, mPV showed higher rates to progress to myelofibrosis and blast phase leading to inferior survival, i.e. a heterogenous MPN [104]. These conflicting complications and their frequency need an explanation. In this cohort, patients may have a longer prodrome that could be responsible for the worse outcome. This assumption is supported by one large study that is not able to confirm these data [105]. A blinded review by a central panel of six hematopathologists confirmed and extended the notion that there were no significant differences concerning BM morphology between mPV and overt stages of PV. Other authors concluded that virtually all cases of mPV were correctly classified as PV according to BM morphology, since there are no significant differences between mPV and overt PV [106]. Overall survival, rate of thrombosis and major bleeding, and probability of transformation was superimposable among patients with masked and overt PV.

In the 5th WHO edition [7] this group of patients were felt to meet the clinical criteria for PV but did not have sufficient erythrocytosis. Thus, to avoid the mPV terminology, a diagnosis of MPN, NOS and close follow-up for emerging PV was recommended.

Finally, an active discussion persists regarding BM biopsy as mandated by the diagnostic criteria [103]. A BM trephine biopsy may not be required in patients with sustained absolute erythrocytosis (Hb concentrations of >18.5 g/dL in men or >16.5 g/dL in women and Hct values of >55.5% in men or >49.5% in women) and the presence of a *JAK2* V617F or *JAK2* exon 12 mutation [107]. However, initial minor MF may present about 20% of patients [107] and even more up to 50% [108] can only be detected by BM, and as argued especially by the ICC [15] this finding may predict a rapid progression to overt myelofibrosis (post-PV myelofibrosis) [109]. Further clarification is needed on the diagnostic and prognostic importance of BM fibrosis at the time of diagnosis since it should be noted that published reports in this regard include cases diagnosed according to 2008 WHO criteria [5] and thus seem to require re-evaluation [15].

PRIMARY MYELOFIBROSIS (PMF)

The International Consensus Classification (ICC) distinguishes "pre-fibrotic" from "overt fibrotic" PMF; the former might mimic ET in its presentation [18, 47, 49]. Most importantly, a high molecular risk profile is associated with a shorter survival not only in overt-PMF but also, when present, in pre-PMF [81, 110]. Approximately 15% of patients with ET or PV might progress into post-ET/PV myelofibrosis (MF) [110].

In terms of semiquantitative MF grading system, both the WHO 5th edition [7] and the ICC [14–16] faithfully follow the approach previously outlined in the former WHO classifications [44, 46]. Both classifications also adopted collagen fibers and osteosclerosis grading.

Pre-fibrotic /early (Pre-PMF)

As shown in Table 3 the question of a more precise definition of early/pre-fibrotic PMF [4] was already evident in 2008/09 [5, 22]; this led to improvements in 2016/17 [6, 12]. The criteria have become universally accepted. However, in regard to pre-PMF vs. ET diagnosis we must acknowledge that in real-world settings there is still a high rate (at least 20%-30%) of misdiagnoses for cases considered as ET while in fact they represent pre-PMF [47, 49]. Regarding the 5th WHO edition [7] maintain as one of the minor criteria on "leukoerythroblastosis "implying the presence of circulating blasts or immature myeloid precursors and nucleated red blood cells. This finding is usually restricted to overt PMF or post-ET/post -PV MF [6, 12, 108]. On the other hand, only in few instances (12%) peripherally circulating blasts ≥ 1% were present in 278 pre-PMF patients [81]. The rare presence of leukoerythroblastosis in pre-PMF was confirmed in a multicentric study of 565 cases. In this study, that was focused on the presence of circulating myeloblasts and erythroblasts median values ranged between 0-2 [47]. In contrast overt PMF often presents with leukoerythroblastosis, with a reported incidence of circulating blasts ≥1% of about 26% [81]. In overt PMF with advanced reticulin/ collagen fibrosis (MF grade 3) [46] erythro/myeloblasts percentages reached 1.7-2.6 / 1.3-2.8 respectively [111] To simplify the diagnostic approach for cases of pre-PMF, the minor criterion of "no or mild leukoerythroblastosis" originally included in older WHO editions that was eliminated in the revised 4th edition of the WHO classification [5, 12] has been revived in the current WHO 5th ed. classification [7].

At clinical presentation about 30-40% of pre-PMF patients manifest significant thrombocytosis closely mimicking ET [28, 48, 49, 76, 79, 112]. Further findings may include mild anemia, leukocytosis with left shifting, elevated lactate dehydrogenase (LDH) levels, whereas significant splenomegaly or anemia with circulating immature white blood cells. Blasts may be seen at a later stage of disease and often indicate disease progression [12, 49, 65, 81, 108, 109]. When analyzing separately patients with pre-PMF and fibrosis grade 0 or 1 compared with those presenting with overt-PMF, i.e. fibrosis grades 2 or 3 [44, 46], an interesting result was unveiled: pre-PMF patients with absent fibrosis (grade 0) differed from those with fibrosis grade 1 for being enriched in females, younger age, higher Hb, and prevalence of IPSS lower risk category [81]. Cytogenetic abnormalities (e.g., +8, −7/7q−, i[17q], inv(3), −5/5q, 12p−, or 11q23) occur in approximately 18% of patients with pre-PMF; These include unfavorable abnormalities in 4%-8% of the cases [81]. The incidence of karyotypic abnormalities in pre-PMF is higher than in ET (5%-10%) and lower than in overt PMF (30%-40%). Median survival in strictly 2016/17 WHO-defined ET [6, 12] has been reported to range from approximately 15 to 22 years [48, 49, 68, 79] as opposed to approximately 11 to 15 years for pre-PMF [49, 79, 81, 110] and therefore a clear cut discrimination of both entities is an essential part of diagnostics [68, 109, 110, 112–117]. In this context, age is by far the most important risk factor for survival. In MPNs median survival in young patients (age ≤ 40 years) was 37 years for PV, 35 for ET and

Table 4. Overt fibrotic primary myelofibrosis (overt PMF) (WHO refs. # [4–7] versus ICC ref. # [14]).

Year Major criteria	2001 Jaffe ES et al. ref. # [4]	2008 Swerdlow SH et al. ref. # [5]	2017 Swerdlow SH et al. ref. # [6]	2024 Akkari Y et al. ref.# [7]	2022 Arber DA. et al. ref.# [14]
Blood	Leukoerythroblastosis, prominent red blood cell poikilocytosis with dacrocytes				
Bone marrow morphology	Reticulin and / or collagen fibrosis, decreased cellularity, dilated marrow sinuses with intraluminal hematopoiesis. Megakaryocytic proliferation and atypia (clustering of megakaryocytes, abnormally lobulated megakaryocytic nuclei, naked megakaryocytic nuclei). New bone formation (osteosclerosis)	Presence of megakaryocytic proliferation and atypia usually accompanied by either reticulin and /or collagen fibrosis	Presence of megakaryocytic proliferation and atypia, usually accompanied by either reticulin and /or collagen fibrosis	Megakaryocytic proliferation and atypia accompanied by reticulin and/or collagen fibrosis grades 2 or 3	Bone marrow biopsy showing megakaryocytic proliferation and atypia, accompanied by reticulin and/or collagen fibrosis grades 2 or 3
Criteria of Exclusion		Not meeting WHO criteria for polycythemia vera, *BCR::ABL1* positive chronic myeloid leukemia, myelodysplastic syndromes or other myeloid neoplasms	Not meeting WHO criteria for polycythemia vera, *BCR::ABL1* positive chronic myeloid leukemia, myeloid dysplastic syndromes or other myeloid neoplasms	WHO criteria for essential thrombocythemia, polycythemia vera, *BCR-ABL1* positive chronic myeloid leukemia, myelodysplastic syndrome, or other myeloid neoplasms are not met	Diagnostic criteria for ET, PV, *BCR::ABL1* positive CML, myelodysplastic syndrome, or other myeloid neoplasms are not met
Clonal genetic abnormality		Demonstration of *JAK2* V617F or other clonal marker (e.g. *MPL* W515K/L), or in the absence of a clonal marker, no evidence that the bone marrow fibrosis or other changes are secondary to infection, autoimmune disorder or other chronic inflammatory condition, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies	Demonstration of *JAK2* V617F or other clonal marker (e.g. *MPL* W515K/L), or in the absence of a clonal marker, no evidence that the bone marrow fibrosis or other changes are secondary to infection, autoimmune disorder or other chronic inflammatory condition, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies	*JAK2*, *CALR*, or *MPL* mutation or presence of another clonal marker	*JAK2*, *CALR*, or *MPL* mutation or presence of another clonal marker or absence of reactive myelofibrosis
Minor Criteria	Hematologic parameters: moderate to marked anemia, low, normal, elevated white blood cell count, platelet count decreased, normal or elevated, moderate to marked splenomegaly or hepatomegaly	Leukoerythroblastosis Increase in serum lactate dehydrogenase level Anemia Splenomegaly	Leukoerythroblastosis Increase in serum lactate dehydrogenase level Anemia Splenomegaly	Presence of at least one of the following, confirmed in 2 consecutive determinations: Anemia not attributed to a comorbid condition Leukocytosis ≥ 11 × 10^9/L Splenomegaly detected clinically and/or by imaging Lactate dehydrogenase level above the upper limit of the institutional reference range Leukoerythroblastosis	Anemia not attributed to a comorbid condition Leukocytosis ≥ 11 x 10^9/L Palpable splenomegaly Lactate dehydrogenase level above the above the reference range Leukoerythroblastosis
	Diagnosis requires meeting criteria 1 and 2 and criteria of exclusion	Diagnosis requires meeting all 3 major and 2 minor criteria	Diagnosis requires meeting all 3 major and 2 minor criteria	The diagnosis of overt primary myelofibrosis requires that all 3 major criteria and at least 1 minor criterion are met	The diagnosis overt PMF requires all 3 major criteria and at least 1 minor criterion confirmed in 2 consecutive determinations

WHO World Health Organization, *ICC* International Consensus Classification, *CML* chronic myeloid leukemia, *PV* polycythemia Vera, *ET* Essential Thrombocythemia, *PMF* Primary Myelofibrosis.

20 for PMF; the corresponding values were 22, 22, and 8 years for ages 41-60 years and 10, 11, and 3 years for ages >60 years [118].

Overt fibrotic primary myelofibrosis (overt PMF)

Diagnosis of overt PMF (Table 4) and its distinction from pre-PMF is mostly based on BM morphology while presence of *JAK2, CALR*, or *MPL* mutation, expected in 90% of the patients, is supportive but not essential for diagnosis [119, 120]. In this context, quantity (grades 2/3) but also the quality of fibrosis (reticulin versus collagen) play an important role since perivascular collagen deposits may be found in grade 2 and are obvious in grade 3 fibrosis and often accompanied by osteosclerosis (new bone formation) [44, 46]. It has been confirmed in several studies that in PMF accurate assessment of the degree of fibrosis has a clear prognostic impact [12, 81, 111, 121–123].

Overt PMF, in the past called myelofibrosis with myeloid metaplasia [124–126], often shows leukoerythroblastosis, anisopoikilocytosis, and tear-drop erythrocytes (dacrocytes) associated with progressive anemia and splenomegaly [81, 113, 118, 119]. Further clinical manifestations in PMF include constitutional symptoms (e.g., fatigue, night sweats, fever, cachexia), bone pain, splenic infarct, pruritus, thrombosis, and bleeding [118, 119].

Regarding cytogenetics, abnormal karyotype is observed in 35-40% of patients, which is higher than that reported for pre-PMF [81, 113, 122, 123]. To clarify the prognostic hierarchy of genetic risk factors in overt PMF and to provide a more refined three-tiered cytogenetic risk model the following calculation has been generate : "very high risk "-single/multiple abnormalities of -7, i[17q], inv(3)/3q21, 12p-/12p11.2, 11q-/11q23, or other autosomal trisomy not including +8/ + 9 (e.g., +21, +19); "favorable"-normal karyotype or sole abnormalities of 13q-, +9, 20q-, chromosome 1 translocation/duplication or sex chromosome abnormality including -Y; "unfavorable"-all other abnormalities [113, 127]. According to this model median survivals for very high risk, unfavorable and favorable risk categories were 1.2, 2.9 and 4.4 years and survival impact was independent of clinically derived prognostic systems, driver and *ASXL1/SRSF2* mutations. The current study clarifies the prognostic hierarchy of genetic risk factors in PMF and provides a more refined three-tiered cytogenetic risk model [127].

SUMMARY-UNMET NEEDS

Revision of available evidences requires an awareness that a number of hematopathologists still have difficulties in consistently applying the described diagnostic guidelines for MPNs. Without going into details according to our experience the most frequent reason is lack of familiarity with diagnosing MPN in BM biopsies. Because the PVSG criteria [38, 39] are definitely outdated there may be a need to re-evaluate former studies like the UK-PT1 study and associated conclusions [128]. A possibility would include to validate the well annotated database of the Swedish Cancer Register which includes more than 9000 MPN patients. This enormous data load is harboring the relative survival ratios (RSRs) in the general population showing considerably higher 10–year values when compared with ET (0.68), PV (0.64), and PMF (0.21) [129]. A re- calculation by applying the ICC [14–16] or WHO 2016/17 (revised 4th edition) diagnostic guidelines would be rewarding [6, 12]. The slight to moderate preponderance of female patients in WHO-confirmed ET contrasting pre-fibrotic PMF [47, 49, 76–80], overt PMF and PV is in need for a convincing explanation.

CONCLUSION

An in-depth analysis of the historical development of MPN classifications can provide invaluable insights for clinical management and observational research. Evolution of WHO diagnostic criteria from 2001 (3rd edition) to 2016/17 (revised 4th edition) have included not only lowering of the platelet value necessary to diagnose ET but, following the international acceptance of pre-PMF as an entity, the separation of "true" ET from pre-PMF ("false" ET). Regarding PV criteria the gender-adjusted thresholds for hemoglobin / hematocrit were lowered to diagnose patients earlier in their disease and BM morphology was upgraded becoming one of the major diagnostic criteria. Altogether the primary role of BM morphology in disease classification has been validated and the complementary role of genetic markers for establishing clonality, facilitating subtype designation, and especially disease prognostication well established. A comparison between the 2016/17 revised 4th edition WHO classification, the ICC, and the new 5th edition of the WHO reveals only minimal differences except for leukoerythroblastosis remaining in the diagnostic criteria for pre-PMF in the WHO 5th edition. Although BM morphology is considered a diagnostic cornerstone, the not so great quality of the figures included in the latest 5th WHO edition would not offer much help in reaching a clear-cut diagnosis. This review is a testament to the validity of the MPN diagnostic approach as developed over more than 22 years by a group of dedicated clinicians, pathologists, and scientists.

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AUTHOR CONTRIBUTIONS

JT drafted the paper including the tables, AO drafted the paper including the tables, UG drafted the paper including the tables, HMK critically appraised and revised its content, DAA critically appraised and revised its content, AT critically appraised and revised its content, TB critically appraised and reviewed the manuscript, AMV critically appraised and reviewed the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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