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Clinical impact of bone marrow morphology for the diagnosis of essential thrombocythemia: comparison between the BCSH and the WHO criteria

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Essential thrombocythemia (ET) is currently diagnosed either by the British Committee of Standards in Haematology (BCSH) criteria that are predominantly based on exclusion and not necessarily on bone marrow (BM) morphology, or the World Health Organization (WHO) criteria that require BM examination as essential criterion. We studied the morphological and clinical features in patients diagnosed according either to the BCSH ($n = 238$) or the WHO guidelines ($n = 232$). The BCSH-defined ET cohort was re-evaluated by applying the WHO classification. At presentation, patients of the BCSH group showed significantly higher values of serum lactate dehydrogenase and had palpable splenomegaly more frequently. Following the WHO criteria, the re-evaluation of the BCSH-diagnosed ET cohort displayed a heterogeneous population with 141 (59.2%) ET, 77 (32.4%) prefibrotic primary myelofibrosis (prePMF), 16 (6.7%) polycythemia vera and 4 (1.7%) primary myelofibrosis. Contrasting WHO-confirmed ET, the BCSH cohort revealed a significant worsening of fibrosis-free survival and prognosis. As demonstrated by the clinical data and different outcomes between WHO-diagnosed ET and prePMF, these adverse features were generated by the inadvertent inclusion of prePMF to the BCSH group. Taken together, the diagnosis of ET without a scrutinized examination of BM biopsy specimens will generate a heterogeneous cohort of patients impairing an appropriate clinical management.

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INTRODUCTION

Accurate diagnosis of essential thrombocythemia (ET) is normally accomplished by applying either the recently updated British Committee for Standards in Haematology (BCSH) guidelines[1,2] or the World Health Organization (WHO) criteria.[3] This, however, continues to be a controversial and challenging issue. The WHO classification places considerably more weight on bone marrow (BM) morphology as a major diagnostic criterion,[3] which contrasts to the BCSH guidelines[1,2] that are mainly focused on an exclusion of the other subtypes of myeloproliferative neoplasm (MPN) or myelodysplastic syndromes (MDS). Consequently, the first set of BCSH diagnostic criteria (A1–A3) allows ET diagnosis without BM biopsy examination by the following criteria: A1-sustained platelet count $>450\times10^9$/l; A2-presence of an acquired pathogenetic mutation; A3-no other myeloid malignancy, especially polycythemia vera (PV), primary myelofibrosis (PMF), chronic myeloid leukemia or MDS.[1] This definition represents a major difference from the WHO classification.[3] However, performance of a BM biopsy is included in the second set of the BCSH criteria (A1 +A3 – A5). In addition to the threshold value of the platelet count (A1) and exclusion of another myeloid malignancy (A3), these criteria require no reactive cause for thrombocytosis and normal iron stores (A4) and also BM morphology (A5) as diagnostic feature ('BM aspirate and trephine biopsy showing increased megakaryocyte numbers displaying a spectrum of morphology with predominantly large megakaryocytes with hyperlobulated nuclei and abundant cytoplasm. Reticulin is generally not increased (grades 0–2/4 or grade 0/3)').[1,2] Performance of a BM biopsy is recommended in cases where there are atypical features, if a change in management is planned during the course of treatment (such as change of cytoreductive therapy), or if transformation into myelofibrosis is suspected.[1] In this context, the challenging differentiation of ET from major subtypes of MPN with presenting thrombocytosis is needed, and it is clinically important to be defined correctly already at diagnosis.[4–7] This concerns particularly PV that is excluded according to the BCSH by revealing a normal hematocrit (Hct) in an iron-replete patient[8,9] and PMF. Following the BCSH criteria,[1,2] PMF is defined as showing a significant BM fibrosis and palpable splenomegaly, blood film abnormalities (circulating progenitors and tear-drop cells) or unexplained anemia consistent with overt myelofibrosis with myeloid metaplasia (MMM).[10,11] Conversely, the prodromal stages, that is, prefibrotic PMF (prePMF), which often present with conspicuous thrombocytosis[12–15] but fail to meet the diagnostic signs and symptoms characterizing MMM,[10] have to be addressed in context with MPN. Further, clinically, it is well known that a small fraction of PV patients may present initially with hemoglobin (Hb) and Hct levels that do not fulfill the 2008 threshold criteria,[16–18] but a

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platelet count that is within BCSH- and WHO-defined ET criteria,[1,2] thus mimicking phenotypically ET at onset.[13,19,20]

The aim of this study was to investigate the clinical presentation and prognostic relevance of BM morphology for ET diagnosis by comparing those criteria as defined by the WHO classification[3] with the first set (A1–A3) of the original and 2014 updated BCSH criteria that do not include BM evaluation.[1,2]

SUBJECTS AND METHODS

A clinico-pathological database currently including 626 patients who were diagnosed and treated for MPN was created by clinicians and hemato-pathologists in the Departments of Hematology and Clinical Pathology at the Medical University of Vienna, Austria. Currently, the associated institutions are centers located in Vienna, Graz, Wels and Linz. Eligibility criteria for entry into this database include diagnosis between 1982 and 2015 with suspected MPN, well-documented clinical follow-up and mutation status (Table 1). Mutation analysis included allele-specific polymerase chain reaction techniques to screen for Janus kinase 2 (*JAK2)*, calreticulin exon 9 (*CALR*) and myeloproliferative leukemia virus oncogene (*MPL*) mutations. A further essential aspect for entry was the availability of representative, initial, treatment-naive BM biopsies (hematoxylin-eosin staining and silver impregnation after Gomori). Iron stores were assessed either by clinical parameters (serum ferritin, mean corpuscular volume of red blood cells) and/or special staining (Prussian blue) of smears. The latter were also used in a very few cases with borderline to slight anemia to exclude MDS with ring sideroblasts, that is, refractory anemia with ring sideroblasts associated with marked thrombocytosis (RARS-T). In cooperation with the local hematopathologists, BM biopsies were centrally re-reviewed under a multi-headed microscope by three of the authors (JT, LM, C B-Sch) who were blinded to initial data (except for age and gender) at entry and outcome. Final diagnosis according to the 2008 WHO criteria was made based on the histopathology review and clinical data.

For the purpose of the present study, we selected all patients with a sustained platelet count $\geqslant 450\times10^9$/l, no evidence for a reactive cause for thrombocytosis and normal iron stores and *BCR-ABL1* negativity. We then applied the WHO-defined ET criteria including BM biopsy evaluation as major diagnostic criterion,[3] and the first set of the 2014 updated BCSH criteria for ET (A1–A3) that require no BM biopsy examination to these patients.[1,2] The WHO criteria consist of a platelet count $\geqslant 450\times10^9$/l, BM biopsy examination, the exclusion of other myeloid neoplasm, and the presence of a clonal marker or the exclusion of reactive thrombocytosis. The first set of the BCSH guidelines (A1–A3) allow diagnosis of ET with the presence of a platelet count $\geqslant 450\times10^9$/l, the presence of an acquired pathogenic mutation (for example, *JAK2*, *CALR* or *MPL*) and no other MPN or MDS.

These two cohorts were compared regarding their presenting clinico-pathological findings, prognosis and adverse events during follow-up.

The diagnosis of post-ET myelofibrosis was made using the IWG-MRT criteria[21] and corresponding clinical and morphological features. These included worsening of anemia (at least a decrease by >2 g/dl from baseline Hb level), increase in splenomegaly either of newly palpable splenomegaly or >5 cm from baseline, overt leuko-erythroblastosis or anisopoikilocytosis with tear-drop erythrocytes, and an overt grade 2/3 reticulin/collagen BM fibrosis in sequential BM biopsies[22] consistent with manifest MMM.[11] Leukemic transformation met criteria for acute myeloid leukemia according to the WHO definition.[23]

Table 1. Distribution of diagnoses in the Austrian database of 626 WHO-classified patients with MPN

	WHO-classified cohort (n = *626)*
ET	259 (41.4%)
prePMF	225 (36.0%)
PV	116 (18.5%)
PMF	22 (3.5%)
MPN-U	4 (0.6%)

Abbreviations: ET, essential thrombocythemia; MPN-U, myeloproliferative neoplasm-unclassifiable; PMF, advanced PMF; prePMF, prefibrotic primary myelofibrosis; PV, polycythemia vera.

Cytoreductive drugs included predominantly hydroxyurea, anagrelide and interferon-alpha or, very rarely, busulphan, pipobroman, P32 or other cytoreductive agents (for details, see Table 2). Many patients received more than one drug during treatment; however, only minor differences could be ascertained between WHO- versus BCSH-confirmed ET. Antithrombotic therapy with low-dose aspirin was applied in 160 patients of the WHO-confirmed ET and 189 patients of the BCSH-defined ET cohort.

Statistical analysis regarded disease-relevant parameters considered at diagnosis. Differences in the distribution of continuous variables between categories were analyzed by the Mann–Whitney *U*-test. Patient groups with nominal variables were compared by Fisher's exact *t*-test. Survival curves were calculated using the Kaplan–Meier method, differences in survival were assessed using the log-rank test. Two-sided *P*-values <0.05 were considered significant.

The study protocol was approved by institutional research ethics committee of the Medical University of Vienna, and written informed consent was obtained from all patients in accordance with the Declaration of Helsinki.

RESULTS

From our Austrian MPN database, which at present includes 626 patients, we recruited 232 (37.1%) cases that according to the WHO criteria were diagnosed as ET and fulfilled the other eligibility criteria, whereas 238 (38.0%) patients met the BCSH criteria A1–A3. Patients that had a follow-up of <1 year ($n=27$) were not included. At diagnosis, both ET cohorts contained a higher proportion of female patients (Table 2). Patients in the BCSH group displayed higher serum lactate dehydrogenase levels (221 vs 207 U/l, $P<0.001$) and had palpable splenomegaly more frequently (16.4% vs 11.9%, $P=0.183$). Differences in the mutation status or therapeutic modalities were not present. The WHO-diagnosed ET cohort contained 18 (7.8%) triple-negative patients. Cytogenetic BCR-ABL1 testing as recommended by the WHO and BCSH was negative in all cases.

The re-classification of 238 patients with BCSH-confirmed ET diagnosis according to the WHO criteria revealed a heterogeneous population, including 77 (32.4%) prePMF and a small cohort of 16 (6.7%) PV cases (Table 3). BM biopsy specimens in the prePMF group showed reticulin fiber grade 1 on a three-graded scoring system in 20 (8.4%) cases, which was not found in the WHO-ET group. In the 16 PV cases, iron deficiency was excluded by showing normal levels of serum ferritin and a normal mean corpuscular volume of the red blood cells. In a few suspicious cases (6/16), an increased red cell mass was found in four confirming the diagnosis, and in 11 of the 16 PV patients the need for phlebotomy was documented in the follow-up. The four PMF patients displayed only fiber grade 2 in their BM associated with thrombocytosis, but no anemia or splenomegaly or blood film abnormalities and therefore were not compatible with MMM or the BCSH criteria for overt PMF.[1,2] Finally, the discrepancy in the number of WHO-confirmed ET cases in the BCSH versus WHO group ($n=91$) is due to the WHO criteria not requiring the presence of an acquired pathogenic mutation ($n=28$) and further included the group of triple-negative cases ($n=18$) and unknown mutation status ($n=45$) as well.

During follow-up of 3290 patient years (median 8.18 years per patient), fibrosis-free (Figure 1a) and overall survival (Figure 1b) were significantly more favorable ($P=0.029/P=0.033$) in the WHO-defined ET cohort. This finding is likely linked with the inclusion of many prePMF cases in the BCSH-confirmed ET group, which implies a worsening of hematological parameters and outcome. This can be demonstrated by comparison of the WHO-diagnosed ET with the prePMF group (Table 4), particularly concerning fibrosis-free survival (Figure 1c, $P=0.015$) and overall survival (Figure 1d, $P=0.019$). Cumulative risk rates for death were 6.0% vs 8.0%, 17.5% vs 21.9% and 27.3% vs 36.5% after 5, 10 and 15 years, respectively. The cumulative rates for post-ET MF was 2.1% vs 5.3%, 6.4% vs 13.3% and 13.4% vs 23.6% at years 5, 10 and 15

Table 2. Clinical characteristics, molecular analysis and constitutional symptoms of patients with ET at presentation and treatment according to applied diagnostic criteria

	BCSH-defined ET (criteria A1-A3)[1,2]	*WHO-defined ET criteria*[3]	P-*value*
General characteristics			
n	238	232	
Age at diagnosis (years)	61.3 (18.8–88.8)	57.2 (17.5–88.8)	0.073
Sex male/female	86/123	93/139	0.750
Clinical characteristics[a]			
Platelets ($\times 10^9$/l)	769 (452–2530)	754 (450–2490)	0.539
Hemoglobin (g/dl)	14.2 (8.6–17.3)	14.4 (8.6–17.3)	0.826
Hematocrit (%)	42.9 (42.9–52.0)	42.7 (29.9–52.6)	0.630
WBC ($\times 10^9$/l)	9.4 (2.21–31.32)	8.82 (2.21–22.3)	0.057
LDH (U/l)	221 (118–763)	207 (104–763)	<0.001
Palpable splenomegaly (218/238)[b]	16.4% (39)	11.9% (26)	0.183
Fibrosis grading $\geqslant 1$	8.4% (20)	0.0% (0)	<0.001
Molecular characteristics			
Pathogenetic mutation present (169/238)[b]	100% (238)	72.8% (169)	—
JAK2 V617F (220/238)[b]	72.7% (173)	80.5% (136)	0.016
CALR (141/181)[b]	32.0% (58)	16.0% (27)	0.011
MPL (53/75)[b]	9.3% (7)	3.6% (6)	0.771
Symptoms at diagnosis			
Constitutional symptoms (169/200)[b]	16.0% (32)	14.8% (25)	0.774
Weight loss	4.5% (9)	4.1% (7)	1.000
Night sweats	8.5% (17)	8.3% (14)	1.000
Fatigue	5.0% (10)	5.9% (10)	0.818
Pruritus (175/202)[b]	2.0% (4)	2.3% (4)	1.000
Cytoreductive Therapy (164/191)[b]			
Hydroxurea	42.9% (82)	42.1% (69)	0.494
Interferon-alpha	34.6% (66)	30.5% (50)	0.429
Anagrelide	30.4% (58)	34.1% (56)	0.494
JAK1/2-Inhibitor	4.7% (9)	3.0% (5)	0.586
Busulfan	2.6% (5)	2.4% (4)	1.000
Others[c]	4.2% (8)	0.6% (1)	0.042
Antithrombotic therapy with low dose aspirin (160/189)[b]	90.5% (171)	88.8% (142)	0.602

Abbreviations: BCSH, British Committee of Standards in Haematology; CALR, calreticulin exon 9 mutations; ET, essential thrombocythemia; JAK2, Janus kinase 2; LDH, serum lactate dehydrogenase; MPL, myeloproliferative leukemia oncogene; WBC, white blood cell count. [a]Median, range. [b]Number evaluable in each cohort. [c]Pipobroman, P32 and other cytoreductive agents.

Table 3. Differentiation and comparison of the BSCH-defined cohort of ET patients[1,2] by applying the diagnostic criteria of the WHO classification[3]

	BCSH-defined ET (n = *238*)	*WHO-defined ET* (n = *232*)
ET	141 (59.2%)	232 (100%)
prePMF	77 (32.4%)	0
PV	16 (6.7%)	0
PMF	4 (1.7%)	0

Abbreviations: BCSH, British Committee of Standards in Haematology; ET, essential thrombocythemia; PMF, advanced PMF; prePMF, prefibrotic primary myelofibrosis; PV, polycythemia vera.

years, respectively. No acute leukemia was seen in the first 5 years of follow-up, after 10 years the rates were 0.9% vs 2.1% and 8.0% vs 4.4% after 15 years.

However, it may be argued that the comparison between the BCSH- versus WHO-defined ET cohorts should be restricted to the ET cases considered in both groups. Noting that the 91 surplus ET cases of the WHO group lacking mutation analysis or who were triple-negative would presumably be recommended to undergo a BM biopsy by following the diagnostic guidelines of the BCSH (A1+A3–A5), a corresponding re-calculation of these patients was performed. This showed that there is a trend for a more favorable overall survival (median difference 2.7 years) but no significance ($P=0.185$) and a comparable tendency regarding fibrosis-free survival ($P=0.241$), if we restrict our calculation to the identical ET cohorts. However, we have to keep in mind that this procedure is not strictly consistent with the first set of the BCSH diagnostic criteria (A1–A3) on which we focused in the present study. Interestingly, if we regarded only the 18 patients that were triple-negative according to their mutational status and compared these 189 WHO-defined ET cases with the BCSH group, overall survival turned out to be significantly different ($P=0.028$), whereas fibrosis-free survival revealed only a tendency ($P=0.071$).

DISCUSSION

This comparative study elucidates differences between the two major classification systems for diagnosis of ET; the data presented here provide evidence that the first set of criteria proposed by the BCSH[1,2] fails to differentiate accurately between WHO-defined ET and prePMF.[14,24,25] Controversy persists whether prePMF is an independent entity, which requires distinction from ET.[1] However, overall application of the WHO-defined BM criteria[23] on larger cohorts of patients, either blindly or explicitly in context with clinical data, has resulted in consensus rates ranging between 76% and $>90\%$ largely depending on study design (all subtypes of

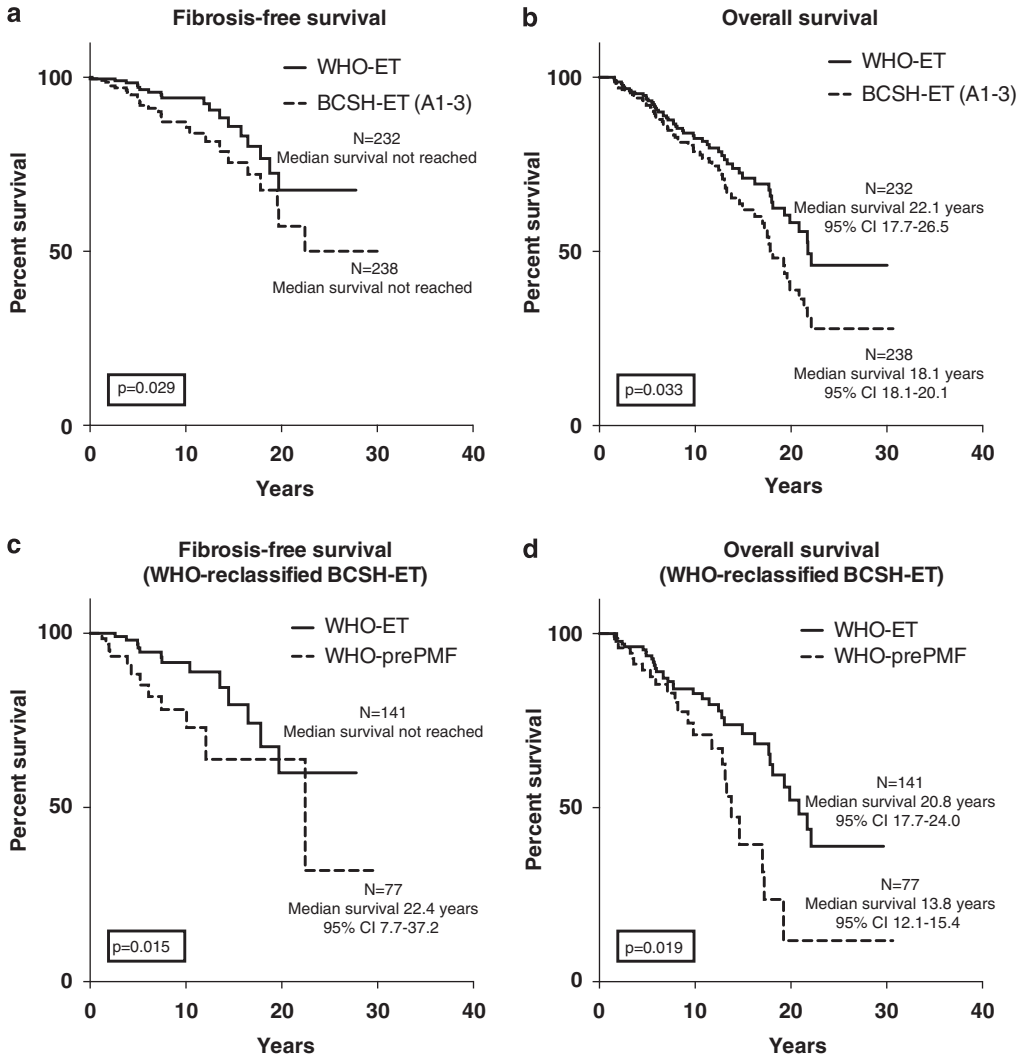

Figure 1. (**a**–**d**) Kaplan–Meier estimates of fibrosis-free survival and overall survival with significant differences in 232 WHO-confirmed versus 238 BCSH-defined ET patients (Figures **a** and **b**). Separate analysis of the WHO-diagnosed prePMF fraction of 77 patients included in the BCSH-classified ET cohort of 238 patients reveals a significant worsening of fibrosis-free and overall survival (Figures **c** and **d**). Abbreviation: CI, confidence interval.

MPN, inclusion of control cases with reactive changes, restriction to single BM features or only ET versus PMF, blinded evaluation or consideration of clinical data).[7,14,24–27] Contrasting these supportive findings, several groups[28–31] failed to reproduce the WHO diagnostic guidelines, likely because of improper application of guidelines and/or small biopsy specimens.[32] Taken together, ~10–15% of patients may present with unclassifiable MPN.[7,26]

Although the second set of ET diagnostic criteria (A1+A3–A5) by the BCSH[1,2] includes BM morphology, it fails to recognize the other hematopoietic cell lineages besides megakaryocytes and fibers ('A5 BM aspirate and trephine biopsy showing increased megakaryocyte numbers displaying a spectrum of morphology with predominantly large megakaryocytes with hyperlobulated nuclei and abundant cytoplasm. Reticulin is generally not increased (grades 0–2/4 or grade 0/3)'). Although the corresponding description in the text is more detailed, the statement that reticulin is generally not increased (grade 0–2 in a four-graded scheme[33] or grade 0 in a three-graded scheme[22]) may be the source of confusion. It applies only to score 0/3 but does not fully equal score 0–2/4, which is consistent with a minor increase. In overt PMF, reticulin fibrosis is explicitly defined as being increased (⩾grade 2/3 or grade 3/4) and may be accompanied by overt collagen and/or new bone formation.[34–36] Patients with prePMF, however, present most frequently with thrombocytosis and normal or only minor accumulation of BM reticulin (score 0–2/4 or 0–1/3), and are probably not fully recognized by the BCSH[1,2] and thus presumably regarded as ET. This shortcoming is likely to be responsible for the adverse events and unfavorable outcome of this cohort. However, if the second set of diagnostic criteria by the BCSH (A1+A3–A5),[1,2] including BM aspirate and trephine biopsy examination, would have been regarded, it cannot be ruled out that a number of cases may have been recognized as being not consistent with ET.

The finding of a small group of 16 (~7%) PV patients in the BCSH group diagnosed according to the corresponding exclusion criteria[1] and presenting with a normal Hct and no evidence of iron depletion[8,9] is not surprising and underscores the proposal to the WHO to enter BM morphology as a major diagnostic criterion for PV.[37] Persuasive evidence has been provided that in patients not meeting the required Hct thresholds for the diagnosis of PV according to the BCSH,[8,9] the diagnosis of so-called masked PV can be established,[17,18] and that in this context BM morphology has an important role.[12,20,38,39] Determination of *JAK2/CALR* mutation status alone, without BM morphology examination, is

Table 4. Clinical characteristics of patients with WHO-defined ET compared with WHO-defined prefibrotic primary myelofibrosis (prePMF) at presentation as derived from the BCSH-confirmed ET cohort

	WHO-defined ET[3]	*WHO-defined prePMF*[3]	P-*value*
General characteristics			
n	141	77	
Age at diagnosis (years)	58.9 (18.8–88.8)	64.6 (23.2–88.1)	0.083
Sex; male/female	58/83	27/50	0.486
Clinical characteristics[a]			
Platelets ($\times 10^9$/l)	725 (452–1836)	840 (457–2530)	0.012
Hemoglobin (g/dl)	14.5 (11.5–17.3)	13.9 (8.6–16.6)	0.007
Hematocrit (%)	43.0 (33.2–52.0)	41.6 (27.5–48.9)	0.036
WBC ($\times 10^9$/l)	8.8 (2.2–21.1)	10.3 (4.0–31.3)	0.004
LDH (U/l)	209 (110–763)	270 (136–598)	<0.001
Palpable splenomegaly (141/77)[b]	9.9% (14)	23.4% (18)	0.009
Fibrosis grading $\geqslant 1$	0.0% (0)	20.8% (16)	<0.001
Molecular characteristics			
Pathogenetic mutation present (141/77)[b]	100% (141)	100% (77)	—
JAK2 V617F (141/77)[b]	70.9% (100)	61.0% (47)	0.011
CALR (99/65)[b]	27.3% (27)	41.5% (27)	0.064
MPL (33/37)[b]	12.1% (4)	8.1% (3)	0.699
Symptoms at diagnosis			
Constitutional symptoms (111/71)[b]	15.8% (16)	20.3% (10)	1.000
Weight loss	3.6% (4)	7.0% (5)	0.315
Night sweats	8.1% (9)	4.2% (3)	0.372
Fatigue	5.4% (6)	5.6% (4)	1.000
Pruritus (111/71)[b]	1.8% (2)	1.4% (1)	1.000
Cytoreductive therapy (108/63)[b]			
Hydroxyurea	45.4% (49)	38.1% (24)	0.423
Interferon-alpha	31.5% (34)	34.9% (22)	0.736
Anagrelide	33.3% (36)	28.6% (18)	0.610
JAK1/2-inhibitor	4.6% (5)	6.3% (4)	0.727
Busulfan	1.9% (2)	3.2% (2)	0.626
Others[c]	0.9% (1)	6.3% (4)	0.062
Antithrombotic therapy with low-dose aspirin (106/63)[b]	89.6% (95)	88.9% (56)	1.000

Abbreviations: BCSH, British Committee of Standards in Haematology; CALR, calreticulin exon 9 mutations; ET, essential thrombocythemia; JAK2, Janus kinase 2; LDH, serum lactate dehydrogenase; MPL, myeloproliferative leukemia oncogene; WBC, white blood cell count. [a]Median, range. [b]Number evaluable in each cohort. [c]Pipobroman, P32 and other cytoreductive agents.

not sufficient to differentiate PV from *JAK2*-mutant ET.[40] It has been demonstrated that Hct threshold values in these patients were significantly higher than in *JAK2*-positive ET revealing a best cutoff for discrimination at 49% in males and 48% in females.[41] Moreover, many of these patients developed signs and symptoms (raising Hct/Hb levels and need for phlebotomies) of overt PV during follow-up.

The distinction of WHO-ET and prePMF, specifically concerning clinical presentation, bleeding events and prognosis, has been shown to be of high clinical relevance.[34,35,42–45] In a multicenter study on 1104 patients, Barbui *et al.*[26] validated the clinical relevance of a strict adherence to the WHO criteria, in particular BM morphology[46] in the diagnosis of ET. They provided important information on presenting hematological features, disease complications and survival in ET versus prePMF. Contrasting these findings, a recent study on a small cohort of 20 young patients (age between 16 and 40 years) with prePMF versus 197 patients with WHO-defined ET failed to confirm these differences and questioned the central role of histological diagnosis for the clinical management and prognostication in young prePMF/ET patients.[47] In this context, a conflicting opinion exists whether the differentiation between WHO-defined ET and prePMF has an impact on treatment modalities in these two entities. Although an only thromboreductive treatment or treatment with low-dose aspirin in WHO-confirmed ET may be successful in the prevention of thromboembolic and hemorrhagic complications,[48] a more aggressive treatment approach using hydroxyurea seems necessary in BCSH-diagnosed ET to prevent thrombosis and transformation to overt myelofibrosis.[49] This suggests that BCSH-defined ET diagnosed by the first set of criteria (A1–A3) includes a considerable fraction of misclassified patients with a more aggressive MPN, very similar to prePMF. This is also reflected by the presence of splenomegaly and elevated serum lactate dehydrogenase levels in our BCSH cohort, which are both features of WHO-classified prePMF. This entity is usually associated with an elevated white blood cell count, which constitutes a major risk factor for arterial thrombosis,[50] increased bleeding tendency,[43] transformation to overt myelofibrosis and a shorter survival.[26]

In conclusion, accurate diagnosis of WHO mandates a scrutinized examination of BM biopsy specimens as key feature. Classification schemes that fail to or do not precisely regard this postulate will end up with a heterogeneous, inadequately defined cohort of patients impairing an appropriate clinical management.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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HG, JT and GJ designed the research, contributed patients, participated in data analysis and interpretation and wrote the paper. GJ performed the statistical analysis. JT reviewed all BM histopathology. All other authors either contributed patients or participated in reviewing bone marrow morphology. All the authors viewed the clinical data, and read and approved the final draft. HG and GJ contributed equally to this work.

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