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Equivalence of BCSH and WHO diagnostic criteria for ET

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933 words
To the editor:

We read with interest the paper from Gisslinger and colleagues (1) who re-examined a group of patients and applied the World Health Organisation (WHO) and British Committee for Standards in Haematology (BCSH) diagnostic criteria for essential thrombocythemia (ET) and evaluated clinical outcomes. They conclude that BCSH defined ET patients (BCSH ET) had worse fibrosis-free survival and prognosis than WHO defined ET (WHO ET), resulting in “inappropriate clinical management”. We find these conclusions misleading and wish to highlight to readers of *Leukemia* a number of problems that raise concerns about the validity of this paper. First and foremost, the analysis is based upon a fundamental failure to correctly apply the BCSH criteria in full. Second, the paper contains multiple factual inaccuracies, methodological deficiencies, and consistently fails to provide balanced data interpretation. Finally, the conclusion that BCSH defined ET “displayed a heterogeneous population”, with the implication that WHO defined ET is more homogeneous, is highly misleading on both molecular and clinical grounds. In the interests of providing a balanced viewpoint, so that readers of *Leukemia* can draw their own conclusions, we tackle these points in detail below.

The fundamental flaw here is the failure to apply the BCSH criteria in full at any stage of the analysis. BCSH diagnostic criteria for ET were first proposed in 2010 (2) and modified in 2014 (3), as shown in table 1. The BCSH criteria were developed because of concerns that the WHO criteria were difficult to apply in a reproducible manner (4). The process used to develop the BCSH guidelines is publically available and follows the grade criteria in weighing and applying evidence. In the absence of a clonal marker (point A2), BCSH criteria require that reactive causes of thrombocytosis should be excluded (point A4) and bone marrow morphology examined for presence of increased megakaryocytes (point A5). In the presence of a clonal marker, BCSH criteria still require that other myeloid malignancies such as primary myelofibrosis (PMF) or myelodysplasia (MDS) are excluded, requiring examination of the bone marrow. Gisslinger and
colleagues apparently misunderstood that presence of a clonal marker does not preclude the need for a bone marrow biopsy. In relation to this, we note that they find higher lactate dehydrogenase levels, and more prevalent palpable splenomegaly in BCSH ET(1). Patients in both BCSH ET and WHO ET groups were anemic (hemoglobin range 8.6-17.3g/dl) and had both surprisingly low and high WBC at diagnosis (WBC range 2.21-31.32 for BCSH ET). The presence of anemia, leucopenia or leukocytosis would have merited a bone marrow biopsy if the BCSH criteria were correctly interpreted. We lament the lack of emphasis upon examination of the blood film in WHO criteria as illustrated in this paper where analysis of this critical tool, clearly highlighted in the BCSH guidelines (Table 1), is hardly mentioned. Further, a raised red cell mass should result in a diagnosis of polycythemia vera (PV) by BCSH criteria and such patients should be excluded from the analysis (Table 1). No information is provided concerning grounds for a diagnosis of PV in 11 cases from the BCSH-ET cohort.

The authors indeed acknowledge that they did not correctly apply the BCSH criteria. In the final paragraph of the results section they state that when data were excluded from 91 patients who lacked a documented mutation, or were triple negative, outcomes were similar for overall survival and fibrosis-free survival for BCSH ET versus WHO ET (p = 0.185 and p = 0.241 respectively). This analysis illustrates that when comparing the same group of patients, there is no meaningful difference in outcome between BCSH ET and WHO ET.

Multiple other methodological problems occur within the paper which should raise concerns. For example, accurate molecular annotation is central to the analysis but, although the methods state that the cohort of patients had well documented mutation status, approximately one quarter of patients in the WHO ET cohort had unknown mutation status. To include such patients in the WHO ET cohort and not in the BCSH ET cohort creates a major bias. Inconsistent interpretation of data is evident from the authors’ suggestion that a difference in median survival of 4 years between BCSH-ET and WHO-ET is significant and clinically meaningful, whereas, in a prior publication by Thiele et al (5), two different cohorts of WHO-defined ET were considered to have “comparable”
outcomes despite a difference in mean survival of 5.1 years. Furthermore, imbalances between the two cohorts are not taken into account: patients in the BCSH ET group were 4.1 years older than WHO ET patients (median age 61.3 versus 57.2 years), an issue that is relevant given the median survival of 18.1 versus 22.1 years; and the presence of JAK2 and CALR mutations were different in BCSH ET and WHO ET. Finally all bone marrow biopsies were reviewed by unblinded consensus which does not address the real problems with application of WHO criteria, identified in multiple independent previous studies for example (6), reviewed in (7). Strangely, the authors also reference the Danish experience in support of the reproducibility of blinded histological evaluation; in reality consensus for histological diagnosis (which is central to the pre-MF disease entity) was only 53% in this series (8).

We believe that clinicians and scientists working in the field will recognize that both BCSH and WHO defined ET consists of a clinically and biologically heterogeneous group of patients with variable risk of disease complications and transformation. Rather than promoting a heavy reliance on poorly reproducible morphological appearances, a more forward thinking approach to define this heterogeneity will be to use molecular analysis to better define patient subgroups and thus refine patient management.

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Table 1
BCSH 2014 Proposed diagnostic criteria for essential thrombocythaemia.

<table>
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<tr>
<th>Diagnosis requires A1–A3 or A1 + A3–A5</th>
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*Polycythaemia vera; excluded by a normal haematocrit in an iron-replete patient.
Myelofibrosis; indicated by presence of significant marrow bone marrow fibrosis (greater or equal to 2/3 or 3/4 reticulin) AND palpable splenomegaly, blood film abnormalities (circulating progenitors and tear-drop cells) or unexplained anaemia.

†Chronic myeloid leukaemia; excluded by absence of BCR-ABL1 fusion from bone marrow or peripheral blood.
Myelodysplastic syndrome; excluded by absence of dysplasia on examination of blood film and bone marrow aspirate.
References


**Errors in the paper for attention of the editor**

1. Numbers of patients male/female in BCSH-defined ET cohort (86/123) does not equal cohort size 209 vs 238.

2. Numbers of patients with JAK2/CALR/MPL mutations are discrepant between Table 2 BCSH cohort and Table 4 patients (even taking into account exclusion of 20 patients. In Table 2 JAK/CALR/MPL mutation positive patients numbered 173/58/7 versus 147/54/7. A difference of 30 patients.

3. Similar inconsistency in numbers of patients on antithrombotic therapy with aspirin = 171 in BCSH patients in Table 2 and 151 in Table 4. Unless none of the 20 excluded patients were taking aspirin there is an error with these data.

4. The methods state that antithrombotic therapy with low dose aspirin was applied in 189 BCSH-ET and 160 WHO-ET patients in comparison with table 2 where the respective figures are 171 and 142.