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To the Editor:

Cytopenia Levels for Aiding Establishment of the Diagnosis of Myelodysplastic Syndromes

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The recent article by Arber et al (1) detailing the 2016 revision of the World Health Organization (WHO) classification of myeloid malignancies and AML was timely and germane. Regarding myelodysplastic syndromes (MDS), the authors indicate diagnostic criteria, which include levels of dysplasia and cytopenias. They further indicated that ethnic variation should be taken into consideration in patients with borderline low neutrophil counts and that a

diagnosis of MDS may still be made in 'rare cases with milder levels of cytopenia' when definitive morphologic and/or cytogenetic features are present (1, 2). The necessity of clarifying these criteria has major relevance, particularly with the advent of recently described group of indolent hematopoietic disorders which may represent precursor states of MDS such as idiopathic cytopenia of unknown significance (ICUS) (3-5), Idiopathic dysplasia of unknown significance (IDUS) (5,6), clonal hematopoiesis of unknown potential (CHIP) (7), and clonal cytopenia of unknown significance (CCUS) (4, 8, 9) that require distinction from MDS. It is recognized that ICUS is not necessarily myeloid (unrecognized lymphoid or plasma cell neoplasms may cause idiopathic cytopenias that may be classified initially as ICUS, and some patients with ICUS may eventuate into non-hematopoietic/reactive disorders such as immune dysregulation), while IDUS is a morphological alteration with many potential causes that do not necessarily influence hematopoiesis in terms of the number of generated cells. These entities have been reviewed in the current NCCN MDS Practice Guidelines 1.2017 (10).

However, although the WHO perspective indicates that 'cytopenia is a *sine qua non* for any MDS diagnosis' (1), the recommended threshold levels of cytopenias they propose for this purpose are those previously reported in the International Prognostic Scoring System (IPSS) risk stratification categorization, that were used for *prognostic but not diagnostic* purposes [hemoglobin (Hb) 10g/dL, absolute neutrophil count (ANC) $1.8x10^9$/L, platelets $100x10^9$/L] (11). As shown in Table 1, providing data from the International Working Group for Prognosis in MDS (IWG-PM) database that was used to generate the Revised-IPSS (IPSS-R) (12), were these levels of cytopenias to be used to diagnose MDS, 18% of MDS patients and 23% of those with <5% marrow blasts, would lack any cytopenia and thus would not be classifiable as MDS. Using standard laboratory values for cytopenias [Hb <13g/dL (males), <12g/dL (females), ANC $<1.8x10^9$/L, platelets $<150x10^9$/L], the data demonstrated that only 1.8% patients evaluated in that study of 7012 MDS subjects would lack a cytopenia (1.3% patients when non-proliferative CMML patients were excluded). Of note, and relevant predominantly for patients with low marrow blast counts in the IWG-PM cohort, the patient's blood counts also needed to demonstrate ≥2 months of stable disease as a potential means of excluding other causes for the cytopenias.

Regarding our main point, it is of relevance that the MDS database (n=816) used to generate the IPSS (11, Table 1) similarly demonstrated that 19% of these patients lacked a cytopenia if defined by the *prognostic level* cutpoints used by the WHO and also incorrectly would not have been considered to have MDS. Similar findings were found in an independent study using these cytopenic cutpoints (13). Prior investigations have demonstrated ethnic-, age- and altitude-related differences in normal hemoglobin levels (14, 15), ethnic-, age- and sex-related differences in platelet levels (16,17), and ethnic- and sex-related differences in platelet and white counts (18). Thus, being cognizant of these conditional blood count variations, we recommend that standard hematologic

values be used to define cytopenias in MDS and believe a modification of the WHO definition of cytopenias as one of the criteria (in addition to definitive morphologic and/or cytogenetic findings) to diagnose MDS would be valuable and most accurate.

Table 1. Cytopenias in MDS

	Cytopenias								
Marrow Blasts	None n	None %	One n	One %	Two n	Two %	Three n	Three %	Total
Less than normal*									
<5%	106	2.3	1946	43	1543	34	950	21	4545
≥5%	19	0.8	421	17	927	38	1100	45	2467
Total	125	1.8	2367	34	2470	35	2050	29	7012
Less than normal, without CMML*									
<5%	73	1.7	1814	43	1395	33	912	22	4194
≥5%	8	0.4	318	15	792	37	1047	48	2165
Total	81	1.3	2132	34	2187	34	1959	31	6359
WHO categorization**									
<5%	1040	23	1988	44	1064	23	453	10	4545
≥5%	197	8	776	32	922	37	572	23	2467
Total	1237	18	2764	39	1986	28	1025	15	7012

*Standard values: Hb <13g/dL (males), <12g/dL (females), ANC <1.8x10^9/L, Platelets <150x$10^{9/}$L

** IPSS values: Hb <10g/dL, ANC <1.8x10^9/L, Platelets <100x10^9/L

Percent (%) values rounded off except for values <3%.

Data obtained from reference 12.

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