To the editor:

**Cytopenia levels for aiding establishment of the diagnosis of myelodysplastic syndromes**


1Stanford University Cancer Institute, Stanford, CA; 2Hanusch Hospital, Boltzmann Institute for Leukemia Research, Vienna, Austria; 3Georg August Universität, Göttingen, Germany; 4Hospital Universitario La Fe, Valencia, Spain; 5University of Texas, MD Anderson Cancer Center, Houston, TX; 6Hospital del Mar, Barcelona, Spain; 7University of Rochester Medical Center, Rochester, NY; 8St. James’s University Hospital, Leeds, United Kingdom; 9Hôpital Avicenne, Assistance Publique-Hôpitaux de Paris(AP-HP)/University Paris XIII, Bobigny, France; 10Hôpital Cochin, AP-HP/University Paris V, Paris, France; 11Heinrich-Heine University Hospital, Düsseldorf, Germany; 12Antonio e Biagio e O C Amigo Hospital, Alassandria, Italy; 13Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Policlinico San Matteo and University of Pavia, Pavia, Italy; 14Institute of Hematology and Blood Transfusion, Prague, Czech Republic; 15Medical University of Vienna, Vienna, Austria; 16The University of Chicago Comprehensive Cancer Research Center, Chicago, IL; 17Quest Diagnostics Nichols Institute, Chantilly, VA; 18Elisabethinen Hospital, Linz, Austria; 19University of Freiburg Medical Center, Freiburg, Germany; 20Cleveland Clinic, Cleveland, OH; 21Federal University of Ceara, Fortaleza, Brazil; 22Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan; 23University Hospital of Innsbruck, Innsbruck, Austria; 24University of Dundee, Scotland, United Kingdom; 25Hospital Universitario Vall d’Hebron, Barcelona, Spain; and 26VU University Medical Center, Amsterdam, The Netherlands

The recent article by Arber et al1 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 that include levels of dysplasia and cytopenias. They further indicated that ethnic syndromes (MDS), the authors indicate diagnostic criteria that include cell neoplasms may cause idiopathic cytopenias that may be classified initially as ICUS, and some patients with ICUS may eventuate into nonhematopoietic/reactive disorders such as immune dysregulation), whereas 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 National Comprehensive Cancer Network MDS Practice Guidelines 1.2017.10

However, although the WHO perspective indicates that “cytopenia is a sine qua non for any MDS diagnosis,” it recommends threshold levels of cytopenias it proposes 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] 10 g/dL, absolute neutrophil count [ANC] $1.8 \times 10^9/L$, platelets $100 \times 10^9/L$).11 Table 1 provides data from the International Working Group for Prognosis in MDS (IWG-PM) database that was used to generate the Revised-IPSS12; if these cytopenia levels were used to diagnose MDS, 18% of MDS patients and 23% of those with <5% marrow blasts would lack any

---

**Table 1. Cytopenias in MDS**

<table>
<thead>
<tr>
<th>Marrow blasts</th>
<th>Cytopenias</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Less than normal</td>
</tr>
<tr>
<td>None, %</td>
<td>1, n</td>
</tr>
<tr>
<td>&lt;5%</td>
<td>106, 2.3</td>
</tr>
<tr>
<td>≥5%</td>
<td>19, 0.8</td>
</tr>
<tr>
<td>Total</td>
<td>125, 1.8</td>
</tr>
<tr>
<td>&lt;5%</td>
<td>73, 1.7</td>
</tr>
<tr>
<td>≥5%</td>
<td>8, 0.4</td>
</tr>
<tr>
<td>Total</td>
<td>81, 1.3</td>
</tr>
</tbody>
</table>

Percent values rounded off except for values <3%. Data obtained from Greenberg et al.12

CMML, chronic myelomonocytic leukemia.

1Standard values: Hb <13 g/dL (males), <12 g/dL (females), ANC <1.8 $\times 10^9/L$, platelets <150 $\times 10^9/L$.

1IPSS values: Hb <10 g/dL, ANC <1.8 $\times 10^9/L$, platelets <100 $\times 10^9/L$.
cytopenia and thus would not be classifiable as MDS. Using standard laboratory values for cytopenias (Hb <13 g/dL [males], <12 g/dL [females], ANC <1.8 × 10^9/L, platelets <150 × 10^9/L), the data demonstrated that only 1.8% of patients evaluated in that study of 7012 MDS subjects would lack a cytopenia (1.3% of patients when nonproliferative chronic myelomonocytic leukemia 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 (Table 1) similarly demonstrated that 19% of these patients lacked a cytopenia if defined by the prognostic level cutoffs 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. Prior investigations have demonstrated ethnic-, age-, and altitude-related differences in normal Hb levels; ethnic-, age-, and sex-related differences in platelet levels; and ethnic- and sex-related differences in platelet and white cell counts. 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 1 of the criteria (in addition to definitive morphologic and/or cytogenetic findings) to diagnose MDS would be valuable and most accurate.

**Contribution:** P.L.G. and H.T. designed the study, analyzed the data, and wrote the report; A.A.v.d.L., D.H., J.M.B., P.F., M.C., and U.G. critically reviewed and approved the manuscript.

**Conflict-of-interest disclosure:** The authors declare no competing financial interests.

**Correspondence:** Peter L. Greenberg, Stanford University Cancer Institute, 875 Blake Wilbur Dr #2335, Stanford, CA 94305-5821; e-mail: peterg@stanford.edu.

**References**


DOI 10.1182/blood-2016-07-728766

© 2016 by The American Society of Hematology

---

To the editor:

**Chronic neutrophilic leukemia in a child with a CSF3R T618I germ line mutation**

Lawrence J. Druhan,1 Daniel P. McMahon,2 Nury Steuerwald,1 Andrea E. Price,1 Amanda Lance,1 Jonathan M. Gerber,1 and Belinda R. Avalos1

1Department of Hematologic Oncology and Blood Disorders, The Levine Cancer Institute, and 2Pediatric Hematology/Oncology, The Levine Children’s Hospital, Carolinas HealthCare System, Charlotte, NC

Chronic neutrophilic leukemia (CNL) is a rare myeloproliferative neoplasm characterized by sustained elevation of neutrophil count, splenomegaly, and poor prognosis. Activating mutations in the colony-stimulating factor 3 receptor (CSF3R), also known as the granulocyte colony-stimulating factor (G-CSF) receptor, have recently been identified in 80% of patients studied with CNL. The most common mutation is T618I, which renders the receptor ligand independent through constitutive JAK/STAT activation. The strong association of activating CSF3R mutations with CNL has led to the addition of a CSF3R T618I mutation or other activating CSF3R mutation to the diagnostic criteria for CNL in the 2016 revision to the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia.
Cytopenia levels for aiding establishment of the diagnosis of myelodysplastic syndromes