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Title:

The degree of anisocytosis predicts survival in patients with primary myelofibrosis

Auhors:

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Abstract:

Introduction: Red cell distribution width (RDW) provides a quantitative measure of anisocytosis and it is associated with the presence of subclinical systemic inflammation and a poor outcome in a variety of diseases when elevated. Anisocytosis is a feature of primary myelofibrosis (PMF) but it's prognostic role in PMF has not yet been evaluated.

Patients and methods: 33 newly-diagnosed patients with PMF were analyzed. Baseline RDW values were obtained in addition to CRP, LDH, complete blood count, iron metabolism parameters and *JAK2* V617F mutational status. Patients were staged according to IPSS prognostic scoring system, liver and spleen size were assessed by palpation.

Results: Median RDW was 19.0% (15.2%-22.5%). RDW correlated significantly with hemoglobin level (p=0.005), CRP (p=0.031), spleen size (p=0.036) and IPSS score (p=0.003). Patients with more pronounced anisocytosis had an inferior overall survival (OS) – very-high RDW (≥19.0%) vs. high RDW (15.1%-18.9%) subgroup, HR 5.37, p=0.002. RDW remained significantly associated with OS (p=0.002) in a multivariate model including IPSS score, hemoglobin level and CRP.

Conclusion: A higher degree of anisocytosis is associated with more advanced disease features and a decreased overall survival. RDW encompasses standard prognostic score and may help in the rapid detection of patients with an unfavorable prognosis.

Keywords:

Anaemia; Hemogram; Inflammation; Myelofibrosis; Splenomegaly

Dear editor,

Primary myelofibrosis (PMF) is a chronic myeloproliferative neoplasm driven by clonal expansion of pluripotent hematopoietic stem cell[1]. An abundance of pro-inflammatory cytokines released by tumor cells leads to reactive fibrosis in bone marrow, production of often bizarre-shaped red cells (dacryocytes) and activation of extramedullary hematopoiesis, mostly in the spleen and the liver. The survival of PMF patients varies from several months to several years and the risk stratification is achieved by several prognostic scoring systems; International Prognostic Scoring System (IPSS)[2] is preferred at the time of diagnosis. IPSS evaluates the initial presence of five risk factors (one point for each: age over 65 years, a hemoglobin level below 100 g/l, white blood cells (WBCs) elevated above 25x10^9/L, 1% or more of circulating blasts and the presence of constitutional symptoms). Red cell distribution width (RDW) is a measure of variability of erythrocyte volume [3] and it is routinely reported by automated cell counters as a part of red blood cell count. It represents a quantitative measure of anisocytosis. The upper normal limit commonly approximates at 15% and this value is also used as a cut-off in our laboratory. An elevated RDW is associated with an increase in mortality and more advanced disease features in the wide spectrum of benign (most notably cardiovascular) and malignant disorders[4-6]. It is reflecting an increase in levels of circulatory cytokines such as IL-6 and hepcidin[7,8] as well as CRP and ESR[9], thus is being recognized as a marker of subclinical systemic inflammation. Anisocytosis is a feature of PMF (where disease pathogenesis supersedes inflammation as its only cause). However the prognostic role of anisocytosis has not yet been studied in patients with PMF or other chronic myeloproliferative neoplasms. In this study, we present the association of increased RDW values with a decreased overall survival in newly diagnosed PMF patients and provide a correlation with disease features and established prognostic score (IPSS).

We analyzed a group of 33 newly diagnosed patients with PMF who presented in our institution in period from 2004 to 2015. The diagnosis was established according to the WHO criteria[10]. Patients with leukemic transformations at time of diagnosis were excluded from this study. Baseline RDW values were obtained in addition to other routine blood analyses (CRP, LDH, complete blood count, serum iron, UIBC, TIBC and ferritin) and JAK2 V617F mutational status. Patients were staged according to IPSS prognostic scoring system, spleen and liver size were assessed by palpation. The Mann Whitney U test, the Pearson correlation and the X^2 test/ the Fisher test were used where appropriate. Survival analyses[11] were performed using methods of Kaplan and Meier, the log-rank test and the Cox regression analysis. All statistical tests were two-sided and P values <0.05 were considered significant. Patients' characteristics are shown in Table 1.

Elevated RDW values were present in all PMF patients with median RDW of 19.0% (range from 15.2% to 22.5%). RDW correlated significantly with hemoglobin level ($r=-0.48$, $p=0.005$), CRP ($r=0.42$, $p=0.031$) and spleen size ($r=0.37$, $p=0.036$). Significant correlation was present between RDW and IPSS score ($r=0.51$, $p=0.003$). No correlation was found according to the age or sex of the patients, degree of bone marrow fibrosis, JAK2 V617F mutational status, WBC, percentage of circulatory blasts, platelet count, MCV, LDH or iron metabolism parameters. This means that both RDW and IPSS are reflecting similar processes

associated with more advanced features of disease. During follow up, considerable variations of RDW in both directions were observed in individual patients and were associated with specific therapy used (hydroxyurea, ruxolitinib, splenectomy, spleen irradiation), disease progression, septic complications, bleeding and transfusion support; thus making RDW an unsuitable parameter to monitor disease activity over time.

The median overall survival (OS) was 42 months with the median follow-up of 28 months. The median RDW value of 19.0% was used as a cut-off to discriminate the "very-high RDW" group (≥19.0%) from the "high RDW" group (15.1%-18.9%) and show significant difference in OS between the two groups (HR 5.37; p=0.002) (Figure 1); the median OS was 23 and 89 months for the " very-high RDW" and the "high RDW" group, respectively.
In univariate Cox regression analysis, RDW (p=0.0026), IPSS score (p=0.0151), CRP (p=0.0025), LDH (p=0.0285) and hemoglobin level (p=0.04) were significantly associated with OS. RDW remained significantly associated with OS (HR=3.16; p=0.002) in a multivariate Cox regression analysis model including IPSS score, CRP, hemoglobin level and RDW (Table 1) and independently contributed to prognosis; choice of variables is based on associations with RDW and OS.

Therefore, RDW represents a good integrative measure of different disease processes and also bears a prognostic significance at the time of PMF diagnosis. It encompasses standard prognostic score (IPSS) and may help in the rapid detection of patients with an unfavorable prognosis. Our preliminary observations are limited by a small number of patients and need to be evaluated by larger studies.

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Table 1.: Characteristics of newly diagnosed patients with primary myelofibrosis. Values are presented as proportions or as median and range. Associations with overall survival in univariate and multivariate Cox regression analysis are shown. *IPSS score used; **IPSS score, Hemoglobin level, CRP and RDW included in a model.

		Univariate survival analysis	**Multivariate survival analysis
Total number	33		
Sex	25 / 33 (76%) males 8 / 33 (24%) females	n.s.	-
Age	68 (57 – 84) years	n.s.	-
Hemoglobin level (g/L)	115 (78 – 165)	HR 0.96; p=0.0409	n.s.
RDW value (%)	19.0 (15.2 - 22.5)	HR 1.68; p=0.0026	HR 3.16; p=0.0022
WBC (x10^9/L)	11.0 (2.1 – 38.7)	n.s.	-
Platelet count (x10^9/L)	366 (56 - 1046)	n.s.	-
≥1% of circulatory blasts	11 / 33 (33%)	n.s	-
CRP (mg/L)	5.65 (0.2 – 73)	HR 1.06; p=0.0255	n.s.
LDH (U/L)	533 (195 – 3400)	HR 1.001; p=0.0285	-
Ferritin (mcg/L)	152 (10 – 721)	n.s.	-
JAK2 V617F positive	21 / 30 (70%)	n.s.	-
Constitutional symptoms present	12 / 33 (36%)	n.s.	-
International prognostic scoring system (IPSS)	Low risk: 3 (9%) Intermediate-1: 10 (30%) Intermediate-2: 9	*HR 2.03; p=0.0151	*n.s.

	(27%) High risk: 11 (33%)		

Figure 1: More pronounced anisocytosis at the time of diagnosis is significantly associated with a decreased overall survival in patients with primary myelofibrosis. Log-rank test; median RDW value (19.0%) is used as a cut-off.