Combining information on C reactive protein and serum albumin into the Glasgow Prognostic Score strongly discriminates survival of myelofibrosis patients

Lucijanić, Marko; Čičić, David; Štoos-Veić, Tajana; Pejša, Vlatko; Rahelić, Dario; Lucijanić, Tomo; Vasilj, Tamara; Ivić, Marija; Sedinić, Martina; Kušec, Rajko

Source / Izvornik: **Blood Cells, Molecules, and Diseases, 2018, 72, 14 - 16**

Journal article, Accepted version
Rad u časopisu, Završna verzija rukopisa prihvaćena za objavljivanje (postprint)

https://doi.org/10.1016/j.bcmd.2018.06.001

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:105:917549

Title: Combining information on C reactive protein and serum albumin into the Glasgow Prognostic Score strongly discriminates survival of myelofibrosis patients

To the Editor:

Primary- (PMF) and secondary-myelofibrosis (SMF) are Philadelphia-chromosome-negative myeloproliferative-neoplasms characterized by strong myeloproliferation and profound inflammatory atmosphere. Myelofibrosis patients often face a significant weight loss and cachexia during disease course. Both elevated C-reactive-protein (CRP) [1, 2] and low albumin [3] were associated with advanced disease features and adverse outcomes in patients with myelofibrosis. The Glasgow Prognostic Score (GPS) [4], developed in patients with non-small-cell lung cancer, integrates information on CRP and albumin. It was associated with poor nutritional and performance status, higher comorbidity and worse prognosis in various cohorts of patients with different malignancies [4, 5]. Clinical and prognostic properties of the GPS were not previously described in the context of myelofibrosis. Therefore, we aimed to investigate prognostic properties of CRP, albumin and the GPS in patients with myelofibrosis and to assess the relationship of the GPS with disease specific features.

We retrospectively analyzed 88 patients with myelofibrosis (67 PMF, 21 SMF) that were evaluated in our institution in period from 2004 to 2018. All patients provided written informed consent for molecular analyses. The study was approved by the Institutional Review Board. Diagnoses were established by the 2016 WHO and the IWG-MRT criteria. Disease specific clinical and hematological parameters were recorded (age, gender, white-blood-cells [WBC], differential-blood-count, circulatory-blasts, hemoglobin, mean-corpuscular-volume [MCV], red-cell-distribution-width [RDW], platelets, mean-platelet-volume [MPV], CRP, lactate-

dehydrogenase [LDH], albumin, serum-iron, total-iron-binding-capacity, transferrin-saturation, ferritin, transfusion-dependency, presence of constitutional-symptoms, degree of bone-marrow-fibrosis, blast-phase disease, spleen and liver size, *JAK2*, *CALR* and *MPL* mutational status). For molecular analyses, DNA was isolated from full blood by QIAamp DNA Blood Mini Kit (Qiagen, ID 51104). *JAK2*-V617F was assessed by allele-specific PCR, *CALR1* and *MPL* exon 10 mutations were screened by high–resolution-melting dye assays and any sample sequence that deviated from normal was Sanger-sequenced. Patients were divided into the GPS risk groups according to the originally proposed method: patients with both CRP>10 mg/L and albumin<35 g/L were given 2 points (poor-risk), patients with only CRP>10 mg/L or albumin<35 g/L were given 1 point (intermediate-risk), whereas patients with both CRP≤10 mg/L and albumin≥35 g/L were given 0 points (good-risk).

Normality of data distribution was tested using the Shapiro Wilk test. Variables were compared between groups using the Mann-Whitney-U test and the χ^2 (Chi-squared) test. Trends of rise or fall in disease specific parameters over the GPS risk groups were tested using the Spearman rank correlation for numerical and the χ^2 test for trend for categorical variables. The Cox-Mantel version of the log-rank test and the Cox-regression-analysis were used to compare survival between groups. Initial survival associations were recognized using the custom made MS Excel workbook [6]. P values <0.05 were considered statistically-significant. Statistical analyses were performed using the MedCalc-Statistical-Software version 18.2.1 (MedCalc Software BVBA, Ostend, Belgium).

Mean age in our cohort was 66.3±11 years, 51/88 (58%) patients were males. A total of 55/88 (62.5%), 28/88 (31.8%) and 5/88 (5.7%) patients were classified as good risk (0 points), intermediate risk (1 point) and poor risk (2 points) according to the GPS, respectively. PMF

and SMF patients did not significantly differ in CRP (median 4.5 vs 3 mg/L; P=0.759) nor albumin (median 43 vs 43 g/L; P=0.517) and were equally distributed among the GPS risk groups (P=0.969). Patients classified into the GPS groups of higher risk expectedly had higher CRP (P<0.001) and lower albumin (P<0.001), but also more frequently had presence of constitutional-symptoms (P=0.004), massive-splenomegaly (P=0.056), blast-phase-disease (P=0.001), presence of circulatory-blasts (P=0.008), higher absolute-monocyte-count (P=0.029), lower hemoglobin (P<0.001), lower platelets (P=0.026), higher LDH (P=0.006), higher RDW (P=0.011), higher ferritin (P<0.001), and more frequently were transfusion-dependent (P<0.001). They were also more likely to belong to the higher Dynamic-International-Prognostic-Scoring-System (DIPSS) risk category (P<0.001). We detected no statistically significant associations of the GPS with *JAK2* (P=0.931), *CALR* (P=0.651), *MPL* (P=0.859) mutational status, degree of bone-marrow-fibrosis (P=0.210), nor with other measured variables (P>0.05 for other comparisons).

As shown in a Figure1a and 1b, both CRP>10 mg/L [hazard-ratio (HR)=3.42; P<0.001] and albumin<35 g/L (HR=4.68; P<0.001) were univariately associated with inferior survival. These associations remained statistically significant in the multivariate model including CRP>10 mg/L (HR=2.49; P=0.013), albumin<35 g/L (HR=2.74; P=0.031) and the DIPSS (HR=2.31; P<0.001). Accordingly, the GPS was able to well distinguish patients with different prognosis as shown in a Figure 1c (overall P<0.001; P<0.001 for all three comparisons between survival curves). The GPS remained statistically significant predictor of inferior survival in the multivariate model including the GPS [intermediate risk GPS (HR=2.08; P=0.040), poor risk GPS (HR=23.52; P<0.001)], the DIPSS (HR=2.72; P<0.001), age (HR=1.02; P=0.298) and male gender (HR=0.77; P=0.443). We further analyzed how the GPS performs after controlling for the individual DIPSS-included factors and observed that the GPS and all factors besides hemoglobin <100 g/L retained statistical significance: GPS (HR=2.68; P=0.004), age>65

years (HR=2.05; P=0.045), WBC>25 x10^9/L (HR=2.7; P=0.014), hemoglobin<100 g/L (HR=0.99; P=0.979), constitutional-symptoms (HR=2.33; P=0.016), circulatory-blasts≥1% (HR=2.38; P=0.013).

Our study identifies the GPS as a strong predictor of inferior survival in myelofibrosis, encompassing valuable prognostic information of metabolic parameters not covered within the DIPSS prognostic system. Patients classified into higher GPS risk groups present with a variety of negative prognostic features representing stronger myeloproliferation, more aggressive disease biology, higher inflammatory status and tendency for iron overload. JAK inhibitors, that are a standard of care for DIPSS intermediate-2- and high-risk patients, can improve inflammatory and nutritional parameters in a subset of treated patients [7] and thus have theoretical potential to reverse negative prognostic impact of the higher GPS. However, patients with higher GPS are also less likely to respond to JAK inhibitors as they pool characteristics predictive on non-response to therapy (lower hemoglobin, lower platelets, larger spleen size [8]). Future studies on larger prospective cohorts of patients are needed to further define the role of the GPS in prognostication of patients with myelofibrosis, especially from the point of view of new and emerging cachexia modulatory drugs.

In conclusion, myelofibrosis patients with higher GPS present with features of more advanced disease. The GPS possesses strong DIPSS-independent prognostic properties and might help in recognition of patients under increased risk of death.

Authors: Marko Lucijanic[a], David Cicic[a], Tajana Stoos-Veic[b,c], Vlatko Pejsa[a,d], Dario Rahelic[d,e], Tomo Lucijanic[e], Tamara Vasilj[a], Marija Ivic[a], Martina Sedinic[a], Rajko Kusec[a,d,f]

Affiliations: [a]Hematology Department, University Hospital Dubrava, Zagreb, Croatia; [b]Department of Clinical Cytology and Cytometry, University Hospital Dubrava, Zagreb, Croatia; [c]University of Osijek, Faculty of Medicine, Osijek, Croatia; [d]University of Zagreb, School of Medicine, Zagreb, Croatia; [e]Endocrinology, Diabetes and Metabolic Disorders Department, University Hospital Dubrava, Zagreb, Croatia; [f]Division of Molecular Diagnosis and Genetics, Clinical Department of Laboratory Diagnostics, University Hospital Dubrava, Zagreb, Croatia.

Corresponding author: Marko Lucijanic, MD PhD, Hematology Department, University hospital Dubrava, Av. Gojka Suska 6, 10000 Zagreb. Tel: +38512902444. Email: markolucijanic@yahoo.com

Conflict of interest: none.

Funding: none

References:

[1] T. Barbui, A. Carobbio, G. Finazzi, P. Guglielmelli, S. Salmoiraghi, V. Rosti, A. Rambaldi, A.M. Vannucchi, G. Barosi, Elevated C-reactive protein is associated with shortened leukemia-free survival in patients with myelofibrosis, Leukemia, 27 (2013) 2084.
[2] G. Barosi, M. Massa, R. Campanelli, G. Fois, P. Catarsi, G. Viarengo, L. Villani, V. Poletto, T. Bosoni, U. Magrini, R.P. Gale, V. Rosti, Primary myelofibrosis: Older age and high JAK2V617F allele burden are associated with elevated plasma high-sensitivity C-reactive protein levels and a phenotype of progressive disease, Leukemia research, 60 (2017) 18-23.
[3] M. Lucijanic, I. Veletic, D. Rahelic, V. Pejsa, D. Cicic, M. Skelin, A. Livun, K.M. Tupek, T. Stoos-Veic, T. Lucijanic, A. Maglicic, R. Kusec, Assessing serum albumin concentration, lymphocyte count and prognostic nutritional index might improve prognostication in patients with myelofibrosis, Wiener klinische Wochenschrift, 130 (2018) 126-133.

[4] L.M. Forrest, D.C. McMillan, C.S. McArdle, W.J. Angerson, D.J. Dunlop, Comparison of an inflammation-based prognostic score (GPS) with performance status (ECOG) in patients receiving platinum-based chemotherapy for inoperable non-small-cell lung cancer, British journal of cancer, 90 (2004) 1704-1706.
[5] D.C. McMillan, The systemic inflammation-based Glasgow Prognostic Score: a decade of experience in patients with cancer, Cancer treatment reviews, 39 (2013) 534-540.
[6] M. Lucijanic, Survival analysis in clinical practice: analyze your own data using an Excel workbook, Croatian medical journal, 57 (2016) 77-79.
[7] R.A. Mesa, S. Verstovsek, V. Gupta, J. Mascarenhas, E. Atallah, T. Burn, W. Sun, V. Sandor, J. Gotlib, Effects of Ruxolitinib Treatment on Metabolic and Nutritional Parameters in Patients With Myelofibrosis From COMFORT-I, Clinical lymphoma, myeloma & leukemia, 15 (2015) 214-221.e211.
[8] K. Menghrajani, P. Boonstra, C. Perkins, K. Gowin, A. Weber, R. Mesa, J. Gotlib, L. Wang, J. Singer, M. Talpaz, Models to Predict Response to JAK-inhibitor Therapy in Patients with Myelofibrosis, Clinical Lymphoma, Myeloma and Leukemia, 17 S358-S359.

Figure 1 Overall survival stratified by **a)** C reactive protein (CRP), **b)** albumin and **c)** the Glasgow prognostic score (GPS) risk groups.