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Title: C reactive protein to albumin ratio as prognostic marker in primary and secondary myelofibrosis

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Abstract:

We retrospectively investigated C reactive protein to albumin ratio (CAR) in a cohort of 142 patients with myelofibrosis [101 primary (PMF); 41 secondary (SMF)] and compared it to hematological and clinical parameters.

Among other associations, higher CAR was significantly associated with higher grade of bone marrow fibrosis, lower frequency of Calreticulin (CALR) mutations, presence of constitutional symptoms, massive splenomegaly, transfusion dependency, blast phase disease, lower hemoglobin, lower platelets, higher ferritin and higher lactate dehydrogenase (LDH) ($P<0.05$ for all analyses). Higher CAR was able to predict inferior survival in PMF independently of DIPSS [hazard ratio (HR)=2.17; $P=0.015$ for high CAR and HR=2.05; $P<0.001$ for DIPSS] and in SMF independently of Mysec-PM (HR=6.48; $P=0.022$ for high CAR and HR=2.63; $P=0.013$ for Mysec-PM) demonstrating its good prognostic potential.

CAR seems to be an independent and prognostically relevant parameter, both in PMF and SMF, and might aid in timely recognition of most vulnerable patients.

Keywords: myeloproliferative neoplasm; myelofibrosis; C reactive protein; albumin; survival

Introduction

Myelofibrosis is a bcr-abl negative myeloproliferative neoplasm (MPN) [1] developing from clonally deranged hematopoietic stem cells. It can develop either as primary disease [primary myelofibrosis (PMF)] or complicating the course of other prior myeloproliferative neoplasm [secondary myelofibrosis (SMF) post polycythemia vera (PV) or essential thrombocytosis (ET)] but with similar clinical features including development of anemia, massive splenomegaly, bone marrow fibrosis and life debilitating constitutional symptoms. Disease is characterized by constitutional activation of JAK-STAT (Janus kinase - Signal transducer and activator of transcription) pathway due to driver mutations in either *JAK2*, *Calreticulin* (*CALR*) or thrombopoietin receptor (*MPL*) genes [2], resulting in profound systemic inflammation often leading to accelerated atherosclerosis and cachexia [3].

In patients with myelofibrosis, both elevated C reactive protein (CRP) and lower albumin are associated with the features of more advanced disease and tendency for worse clinical outcomes, either as individual parameters or as parts of different prognostic scores [4-8]. CRP to albumin ratio (CAR) has been recently recognized as an inflammatory biomarker and prognostic factor in the context of cardiovascular diseases [9] and several malignant neoplasms [10,11]. However, clinical correlations of CAR and its prognostic potential in patients with myelofibrosis or other MPNs have not been investigated so far. Therefore, here we aim to evaluate clinical and prognostic properties of CAR in patients with primary and secondary myelofibrosis.

Patients and methods

We retrospectively investigated a cohort of 142 with myelofibrosis, newly diagnosed [124/142 (88%)] or referred to [17/142 (12.1%)] five hematological centers in our country in period 2004-2020. All patients fulfilled 2016 World Health Organization (WHO) criteria for PMF [1] or 2008 International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) criteria for SMF [12]. All patients provided written informed consent for molecular analyses. The study was approved by the institutional review boards. Patients were staged according to the Dynamic International Prognostic

Scoring System (DIPSS) [13] and the Myelofibrosis Secondary To PV And ET Prognostic Model (Mysec-PM) [14] prognostic scoring systems. Spleen size was assessed by palpation. Massive splenomegaly was defined as spleen palpable >10 cm from the left costal margin. Transfusion dependency was defined as ≥2 red blood cell transfusion units per month within 3-month period prior to inclusion [15]. Bone marrow fibrosis was graded according to the current European consensus [13]. CRP (normal range <5 mg/L) and albumin (normal range 40-48 g/L) levels were determined in addition to other standard hematological and clinical parameters. CAR was calculated as CRP (mg/L) to albumin (g/dL) – i.e. CRP (mg/L) to albumin (g/L) ratio x10.

Normality of data distribution was assessed using the Shapiro Wilk test. All numerical variables had non-normal distribution and were presented as median and interquartile range (IQR) and were compared between groups using the Mann Whitney U test or Kruskal Wallis one-way analysis of variance (ANOVA). Categorical variables were presented as ratio and percentage and were compared between groups using the X2 test. Survival analyses were based on the Kaplan-Meier method. The receiver operating characteristic (ROC) curve analysis using survival status as classification variable was performed for determining an optimal CAR cut-off value for survival analyses. Overall survival was measured from the start of follow-up to the last visit or death of any cause. Survival curves were compared between groups using the Cox Mantel version of the log-rank test. Multivariate survival analyses were performed using the Cox regression analysis. P values <0.05 were considered statistically significant. Data screening for associations with survival was performed using the custom-made MS Excel workbook [16]. Statistical analyses were performed using the MedCalc Statistical Software version 19.2 (MedCalc Software BVBA, Ostend, Belgium).

Results

We analyzed a total of 142 patients with myelofibrosis, 101/142 (71.1%) with PMF and 41/142 (28.9%) with SMF. There were 84/142 (59.2%) male and 58/142 (40.8%) female patients. Median age was 67.5 years, IQR (59.3 - 75). Median CRP was 4.5 mg/L, IQR (1.3 - 11.8) and median albumin was 42 g/l,

IQR (39 - 45). Median CAR was 1.1 IQR (0.3 - 2.9). CAR relationship with patients' clinical characteristics is shown in Table 1.

There was no significant difference in CAR in comparison to age, gender, nor type of myelofibrosis (P>0.05 for all analyses). Myelofibrosis patients with **higher CAR** were statistically significantly more likely to have a **higher grade of bone marrow fibrosis** (59.2% vs 79.5% grade II-III fibrosis in patients below and above median CAR value, respectively; P=0.019), **lower frequency of CALR mutation** (15.5% vs 3.5% for patients below and above median CAR value, respectively; P=0.029), **presence of constitutional symptoms** (28.2% vs 64.8% for patients below and above median CAR value, respectively; P<0.001), **massive splenomegaly** (13.6% vs 35.9% for patients below and above median CAR value, respectively; P=0.002), to be **transfusion dependent** (21.4% vs 37.1% for patients below and above median CAR value, respectively; P=0.041), to have **blast phase disease** (1.4% vs 10.1% for patients below and above median CAR value, respectively; P=0.032), **lower hemoglobin** (median 120 vs 99 g/L for patients below and above median CAR value, respectively; P=0.002), **lower platelets** (median 418 vs 200 $x10^9$/L for patients below and above median CAR value, respectively; P<0.001), **higher LDH** (404 vs 543.5 UI/L for patients below and above median CAR value, respectively; P=0.002), **higher RDW** (median 19.1 vs 20.1% for patients below and above median CAR value, respectively; P=0.006), **higher MPV** (9.1 vs 9.7 fL, for patients below and above median CAR value, respectively; P=0.047), **lower serum iron** (14.8 vs 12.1 mcmol/L for patients below and above median CAR value, respectively; P=0.047),) and **lower total iron binding capacity** (54.4 vs 47.4 mcmol/L for patients below and above median CAR value, respectively; P<0.001). Also**, higher CAR as continuous variable** was present in patients **with ≥1% peripheral blasts** (median CAR 0.62 vs 2.17 in patients with no and present peripheral blasts, respectively; P<0.001) and showed **positive correlation with ferritin levels** (Rho=0.36; P=0.002) and **higher basophil count** (Rho=0.2; P=0.018).

Among PMF patients there was a statistically significant difference in CAR levels between specific **DIPSS categories** (P<0.001), with higher CAR being associated with higher DIPSS categories (Rho=0.47; P<0.001). Similar association was present between CAR and **IPSS** (Rho=0.43; P<0.001) among PMF patients evaluated at the time of diagnosis. In a cohort of SMF patients CAR was

significantly different between **Mysec-PM categories** (P<0.001), with higher CAR being associated with higher Mysec-PM categories (Rho=0.41; P=0.014). Also, CAR was significantly different among different categories of Glasgow prognostic score (GPS) which is derived from CRP and albumin (P<0.001), higher CAR being associated with higher risk GPS categories (Rho=0.79; P<0.001).

A total of 49 patients died during follow-up period, median overall survival was 68 months. Using the ROC curve analysis, we have set the optimal CAR cut-off value for survival discrimination at 2.04 for PMF and 2.45 for SMF patients. In the univariate analyses, higher CAR was able to predict inferior overall survival in both the PMF [hazard ratio (HR) 4.6; P<0.001] and the SMF (HR=7.3; P<0.001) cohorts. Also, statistically significant trends for decreased survival were present in both PMF and SMF cohorts with rising CAR levels stratified at terciles as shown in the Figure 1 (P<0.001 for between-curve difference and for statistical trend in both cohorts).

We have further investigated CAR prognostic properties in several multivariate Cox regression analysis models. Among PMF patients, CAR remained statically significantly associated with inferior overall survival independently of DIPSS score (HR=2.17; P=0.015 for high CAR and HR=2.05; P<0.001 for DIPSS). Similarly, among SMF patients CAR retained prognostic properties in comparison to Mysec-PM score (HR=6.48; P=0.022 for high CAR and HR=2.63; P=0.013 for Mysec-PM). We also investigated whether CAR provides different prognostic information in comparison to GPS. When analyzed together, both CAR and GPS showed mutually independent prognostic properties (HR=2.34; P=0.045 for higher CAR and HR=2; P=0.041 for GPS), showing that although combined from same two parameters (CRP and albumin), these two scores recognize different spectra of prognostic information in patients with myelofibrosis.

Discussion

To the best of our knowledge, our work is first to evaluate clinical associations and prognostic relevance of CAR in myelofibrosis patients. As our data show, higher CAR is associated with unfavorable clinical characteristics and higher predetermined risk of death as assessed by contemporary prognostic scores.

In line with this is an increased hazard for death among patients presenting with higher CAR in both PMF and SMF cohorts, a phenomenon independent of DIPSS and Mysec-PM scores in multivariate survival analyses. This suggests very potent prognostic properties of CAR in these clinical contexts, and ability to better and timely recognize myelofibrosis patients under higher risk of death.

Both elevated CRP and lower albumin reflect inflammatory response of the liver mediated through IL-6, and are often encountered among myelofibrosis patients where systemic inflammation and high IL-6 levels are a feature of the disease [17]. IL-6 exerts its effects either through binding to membrane bound IL-6 receptors in the liver and other cells (classic signaling), or through binding to circulating IL-6 receptors that are shed from cellular surfaces in inflammatory states, subsequently activating signaling cascade in any other tissue where IL-6 and IL-6R complex binds (trans signaling) [18]. Classic IL-6 signaling results in production of acute phase reactants (including CRP) and reduced production of albumin and transferrin in the liver through JAK-STAT3 signaling cascade [19].

In myelofibrosis, higher CRP and lower albumin are associated with features of more advanced disease [7], and combining them into ratio exploits dynamics of both parameters to obtain one-directional measure of disease severity. Higher CAR was associated with a number of DIPSS- and Mysec-PM-contained parameters (lower hemoglobin, peripheral blasts, constitutional symptoms, CALR wild type, lower platelet count), but also with other prognostically unfavorable parameters like higher transfusion dependency, higher LDH, higher ferritin, blast phase disease, higher basophil count, higher RDW and higher MPV. Most interestingly, high CAR patients were more likely to have advanced bone marrow fibrosis and massive splenomegaly which are hallmarks of the disease. Considering associations with parameters of iron metabolism, higher CAR remained associated with lower Fe, lower TIBC and higher ferritin when post-PV SMF patients (who are usually iron-depleted due to phlebotomies or cytaphereses during PV stage of disease) were excluded from analysis (data not shown).

Another CRP and albumin derived score, GPS, seems to differ in prognostic abilities in comparison to CAR in myelofibrosis patients. As we have shown in the current study, GPS and CAR predict survival independently of each other, both remaining significantly associated with worse outcomes. Both scores showed associations with a number of same disease features [7], however in comparison to CAR, GPS

had no statistically significant associations with the degree of bone marrow fibrosis nor with CALR mutational status. Since both CRP and albumin are moderately correlated (Rho= -0.51; P<0.001), CAR might be more sensitive to their relatively small derangements than GPS that is based on scoring predetermined CRP and albumin cut-off levels.

Limitations of our work are retrospective study design, lack of statistical power for some of presented analyses due number of patients in specific subgroups and inability to assess presence of specific mutations commonly associated with myeloid malignancies and their relationship with CAR. This also limits us from comparing CAR to MIPSS70 or GIPSS prognostic scores. However, our results are based on multicentric data and large number of events with good follow-up time. They identify CAR as prognostically relevant parameter in patients with both PMF and SMF, providing additional information to established prognostic scores.

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Table 1: CRP to albumin ratio (CAR) in relationship to patients' characteristics. Patients in the table are divided at median CAR level (1.07) to lower and higher CAR.

	Overall	**Lower CAR**	**Higher CAR**	**P value**
Number of patients	142	71	71	-
CAR	1.1 IQR (0.3 - 2.9)	0.3 IQR (0.1 - 0.5)	2.9 IQR (1.9 - 7.3)	-
Age (years)	67.5 IQR (59.3 - 75)	67 IQR (56.5 - 76)	68 IQR (62 - 74.5)	0.348
Sex				
Male	84/142 (59.2%)	43/71 (60.6%)	41/71 (57.7%)	0.733
Female	58/142 (40.8%)	28/71 (39.4%)	30/71 (42.3%)	
Myelofibrosis type				
PMF	101/142 (71.1%)	53/71 (74.6%)	48/71 (67.6%)	0.355
SMF	41/142 (28.9%)	18/71 (25.4%)	23/71 (32.4%)	
BM fibrosis				
Grade 0-I	45/142 (31.7%)	29/71 (40.8%)	16/71 (22.5%)	**0.019 ***
Grade II-III	97/142 (68.3%)	42/71 (59.2%)	55/71 (77.5%)	
***JAK2* mutated**	97/140 (69.3%)	45/71 (63.4%)	52/69 (75.4%)	0.124
***CALR* mutated**	11/115 (9.6%)	9/58 (15.5%)	2/57 (3.5%)	**0.029 ***
***MPL* mutated**	4/115 (3.5%)	2/58 (3.4%)	2/57 (3.5%)	1.000
Constitutional symptoms	66/142 (46.5%)	20/71 (28.2%)	46/71 (64.8%)	**<0.001 ***
Transfusion dependency	41/140 (29.3%)	15/70 (21.4%)	26/70 (37.1%)	**0.041 ***
Massive splenomegaly	32/130 (24.6%)	9/66 (13.6%)	23/64 (35.9%)	**0.003 ***
Blast phase disease	8/140 (5.7%)	1/71 (1.4%)	7/69 (10.1%)	**0.032 ** **
Spleen size under left costal margin (cm)	4 IQR (1 - 10)	3 IQR (0 - 7.5)	6 IQR (2.8 - 14.3)	**0.002 ** **

	Overall	Lower CAR	Higher CAR	P value
WBC (x10^9/L)	10.5 IQR (6.1 - 17.1)	10.3 IQR (6.1 - 15.9)	11.1 IQR (6.1 - 18.6)	0.466
Peripheral blasts ≥1%	51/142 (35.9%)	21/71 (29.6%)	30/71 (42.3%)	0.115 **
Abs. mono. (x10^9/L)	0.4 IQR (0.2 - 0.7)	0.5 IQR (0.3 - 0.7)	0.4 IQR (0.2 - 1)	0.424
Abs. basophils (x10^9/L)	0.1 IQR (0 - 0.3)	0.1 IQR (0 - 0.2)	0.1 IQR (0.1 - 0.3)	0.148 **
Abs. lymphocytes (x10^9/L)	1.5 IQR (1.1 - 2.1)	1.5 IQR (1.1 - 2)	1.4 IQR (1 - 2.3)	0.819
Hemoglobin level (g/L)	108 IQR (93.3 - 130)	120 IQR (97.5 - 137)	99 IQR (88 - 121)	**0.002** * **
MCV (fL**)**	87.9 IQR (81.7 - 93.7)	88.1 IQR (81.9 - 95.3)	87.2 IQR (81.4 - 93)	0.588
RDW (%)	19.6 IQR (17.9 - 21.5)	19.1 IQR (17 - 20.6)	20.1 IQR (18.9 - 21.9)	**0.006** * **
Platelets (x10^9/L)	317 IQR (164 - 540)	418 IQR (290 - 616)	200 IQR (124 - 382.5)	**<0.001** * **
MPV (fL)	9.4 IQR (8.4 - 10.4)	9.1 IQR (8.3 - 9.8)	9.7 IQR (8.6 - 10.7)	**0.047** * **
LDH (U/L)	473.5 IQR (322.5 - 700)	404 IQR (276.8 - 569.5)	543.5 IQR (350.3 - 800.5)	**0.002** * **
CRP (mg/L)	4.5 IQR (1.3 - 11.8)	1.3 IQR (0.7 - 2.4)	11.9 IQR (7.9 - 28.7)	**<0.001** * **
Albumin (g/L)	42 IQR (39 - 45)	44 IQR (42 - 47)	40 IQR (36.5 - 43)	**<0.001** * **
Fe (mcmol/L)	13.6 IQR (7.3 - 18)	14.8 IQR (10 - 19)	12.1 IQR (5.3 - 15.7)	**0.015** * **
TIBC (mcmol/L)	51.4 IQR (44.4 - 57)	54.4 IQR (48.2 - 60.9)	47.4 IQR (39.5 - 55)	**<0.001** * **

	Overall	Lower CAR	Higher CAR	P value
Transferrin saturation (%)	27.5 IQR (14 - 35.6)	29.2 IQR (19.9 - 37.8)	24.5 IQR (12 - 33.5)	0.257
Ferritin (μg/L)	188 IQR (44.6 - 489)	168.5 IQR (20.5 - 353.8)	232.5 IQR (80 - 541.3)	0.088 **
Creatinine (mcmol/L)	84.5 IQR (71 - 102.8)	84 IQR (71 - 107)	85 IQR (72 - 100)	0.597
Urea (mmol/L)	6.6 IQR (5.2 - 8.1)	6.6 IQR (5.2 - 8)	6.5 IQR (5.6 - 8.1)	0.770
GPS				
Good risk	97/141 (68.8%)	11/17 (64.7%)	86/124 (69.4%)	**P<0.001** * **
Intermediate risk	37/141 (26.2%)	5/17 (29.4%)	32/124 (25.8%)	
Poor risk	7/141 (5%)	1/17 (5.9%)	6/124 (4.8%)	
DIPSS (PMF)				
Low risk	15/101 (14.9%)	14/53 (26.4%)	1/48 (2.1%)	**P<0.001** * **
Intermediate-1 risk	36/101 (35.6%)	21/53 (39.6%)	15/48 (31.3%)	
Intermediate-2	40/101 (39.6%)	16/53 (30.2%)	24/48 (50%)	
High risk	10/101 (9.9%)	2/53 (3.8%)	8/48 (16.7%)	
Mysec (SMF)				
Low risk	3/35 (8.6%)	2/24 (8.3%)	1/11 (9.1%)	**P<0.001** * **
Intermediate-1 risk	12/35 (34.3%)	11/24 (45.8%)	1/11 (9.1%)	
Intermediate-2	10/35 (28.6%)	7/24 (29.2%)	3/11 (27.3%)	
High risk	10/35 (28.6%)	4/24 (16.7%)	6/11 (54.5%)	

* statistically significant at level P<0.05

** statistically significant at level P<0.05 when comparing parameters to CAR as a continuous variable

Figure 1: a) Overall survival in patients with primary (PMF) and **b)** secondary myelofibrosis (SMF) stratified according to the CRP to albumin ratio (CAR) terciles.