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A simple acute phase protein score to predict long-term survival in patients with acute myeloid leukemia.

Original Research Article

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Abstract

High levels of acute phase reactants can be associated with adverse outcome in patients with various solid tumor types. For patients with acute myeloid leukemia (AML), this correlation is unknown. We retrospectively investigated the prognostic value of pretreatment acute phase protein levels in 282 consecutive newly diagnosed AML patients undergoing at least one cycle of intensive induction chemotherapy. We applied a new score integrating pre-treatment C-reactive protein (CRP), fibrinogen, and albumin levels termed the CFA ratio, and we stratified patients into two groups: Patients with a CFA ratio below 3.06 had decisively better progression free (26.2 vs. 7.7 months; *P*<.001), disease free (56.4 vs. 8.7 months; *P*<.001) and overall survival (61.2 vs. 13.8 months; *P*<.001). Results remained significant when adjusting for confounders including ELN risk group. Early mortality also tended to be lower in the low CFA ratio group. Finally, patients with lower modified Glasgow prognostic score (mGPS) similarly had better outcome. In conclusion, our data suggest that an elevated CFA ratio as well as a high mGPS are associated with adverse outcome in patients with newly diagnosed AML undergoing intensive induction. These parameters should undergo prospective evaluation for their contribution to risk profiling in AML patients.

Introduction

The complex interplay between inflammation and cancer development was suggested already in the 19th century[1], and it may best be exemplified by the increased risk for colorectal cancer in patients with chronic bowel disease including Crohn's disease or ulcerative colitis.[2] Therefore, the role of acute phase proteins has not only been investigated during inflammatory disorders, but similarly in malignancies. Among acute phase reactants, C-reactive protein (CRP) and fibrinogen are produced by hepatocytes upon tissue damage or infection through interleukin (particularly IL-6 and IL-1) and TNF-alpha signaling pathways.[3,4] During inflammatory processes, such mediators are elevated, whereas levels of "negative" acute phase reactants such as serum albumin and transferrin decrease due to lowered synthesis or increased degradation.[5] Upon secretion, CRP circulates in the plasma where it recognizes and eliminates pathogens by binding to cells and subsequently activating the complement system[6]. Fibrinogen exerts a key role within the coagulation cascade by mediating platelet aggregation and providing the substrate for clot formation upon conversion to fibrin by thrombin.[7] Serum albumin is the most abundant blood protein and essential for maintaining oncotic homeostasis, as well as serving as a carrier protein for small hydrophobic molecules including steroids, hormones, therapeutic compounds, and toxins.[8,9] Tumor growth can lead to inflammation, which, in turn, can trigger the synthesis of acute phase proteins.[10] CRP is elevated in chronic inflammatory conditions, it can promote tumor growth and may reflect various types of immune responses following presentation of tumor antigens.[11] Inflammatory proteins can also be produced by cancer cells themselves as there is evidence of expression of CRP, IL-6 and IL-8 in various cancer cell types and cell lines.[12–14]

The CRP/albumin ratio has been investigated in various solid tumors including hepatocellular carcinoma,[15] non-small cell lung cancer,[16] ovarian[17] and pancreatic adenocarcinomas.[18] In these studies, high levels of acute phase proteins as expressed by an elevated ratio (high CRP and/or low albumin) were consistently associated with adverse outcome. By allocating points for different levels of CRP and albumin, the Glasgow prognostic score (GPS) and

modified GPS (mGPS) can be used to describe the acute phase protein status of a given patient. It has been shown to have prognostic significance in a variety of solid tumors[19] as well as hematologic malignancies including peripheral T-cell lymphoma,[20] DLBCL[21] or advanced Hodgkin's lymphoma. Moreover, the score has been shown to predict treatment tolerance in patients with head and neck cancer.[22] .

In acute myeloid leukemia (AML) and other hematologic malignancies, pro- and anti-inflammatory cytokines were suggested to be relevant for the pathogenesis and progression of these diseases. Population-based studies indicated that patients with a history of infectious or autoimmune disease had an increased risk of developing AML.[23,24] Dysregulation of cytokine expression, as a hallmark of chronic inflammation and autoimmunity, is promoting the development of hematologic malignancies.[25] Elevated pretreatment CRP levels were associated with adverse outcome in patients with DLBCL in a meta-analysis.[26] We recently reported that elevated fibrinogen levels were associated with adverse survival in newly diagnosed AML patients.[27] Moreover, increased serum ferritin levels were predictive of adverse overall and relapse-free survival in young intermediate-risk AML patients[28] and, also, in a cohort of AML patients when adjusting for CRP levels.[29] Elevated pretreatment CRP and ferritin levels were positively associated with the incidence of systemic inflammation during anti-leukemic induction chemotherapy.[30] Albumin was reported to be an independent prognostic factor and a superior parameter compared to the body mass index to evaluate the nutritional status in newly diagnosed AML patients.[31] To the best of our knowledge, however, no study has investigated so far how CRP or albumin levels at diagnosis may affect survival in AML patients, and the Glasgow prognostic score has not been verified for AML patients. In this study, we aimed to investigate whether levels of acute phase reactants at diagnosis correlate with survival or response to intensive induction chemotherapy in newly diagnosed AML patients. Ultimately, we evaluated the CFA ratio, a novel simple score based on acute phase protein levels, whether it can provide relevant prognostic information in AML patients at diagnosis.

Methods

Patients: This retrospective single-center analysis included data of consecutive patients with a first diagnosis of AML between 2000 and 2018 at the University Hospital of Bern, Switzerland. *De novo* and secondary AML were included. We limited our analysis to AML patients between 18 and 65 years at the time of diagnosis and they had to undergo at least one cycle of intensive chemotherapy with curative intent. Data were collected for gender, age, hemoglobin, white blood cell and neutrophil counts, platelets, bone marrow infiltration and peripheral blasts, C-reactive protein, albumin, fibrinogen, as well as for molecular and cytogenetic abnormalities and for blood and bone marrow assessments following treatment and during follow-up.

Treatment: Patients were treated within or according to the following protocols of the HOVON (Dutch-Belgian hemato-oncology group) and SAKK (Swiss group for clinical cancer research) AML groups: SAKK/ HOVON-42, -81, -92, -102, and -132; or of the APL (French-Belgian-Swiss APL) group: APL-2000 and APL-2006. Induction treatment for AML patients consisted of one or two cycles of cytarabine and an anthracycline (either idarubicin or daunorubicin). Consolidation therapy consisted of either additional cycles of chemotherapy or high-dose chemotherapy followed by autologous or allogeneic hematopoietic stem cell transplantation in favorable or intermediate-risk patients, or in allogeneic transplantation for adverse-risk patients. Patients had to have an Eastern cooperative oncology group performance status of 0-2 and were not previously treated for AML with the exception of hydroxyurea for initial cytoreduction.

Definitions: Response was assessed according to international working group criteria.[32] Morphologic complete remission (CR) was defined as bone marrow blasts of <5% with complete hematologic recovery (neutrophils (ANC) ≥1.0G/L, platelets ≥100 G/L, and no transfusion dependence). Complete remission with incomplete hematologic recovery (iCR) was defined as bone marrow blasts of <5% with neutrophils <1.0 G/L and/or platelets <100 G/L**.** Progression free survival was defined as the time from diagnosis to progression or death

from any cause or last follow-up whichever occurred first. Overall survival was the time between diagnosis and death from any cause or until last follow-up. Disease free survival was the time between CR and relapse or death from any cause or last follow-up. Subjects lost to follow-up were censored at the time last known to be alive. Genetic risk profiling was applied according to the European Leukemia Network (ELN) update from 2017.[33]

Development of a novel acute phase protein score: Reference levels for the serum acute phase proteins were as follows: CRP: <5 mg/L; fibrinogen: 1.8 - 4.0 g/L; and albumin: 35 - 52 g/L. The CRP*fibrinogen/albumin (CFA) ratio was calculated as follows:

$$\frac{\text{CRP (mg/L)} * \text{Fibrinogen (g/L)}}{\text{Albumin (g/L)}}$$

When considered as a numeric value, this index showed positive skew. Therefore, natural logarithms were applied in subsequent analyses, which allowed for a more symmetric distribution. The cutoff was determined using the minimum *P value* approach with multiple log-rank tests. To correct for increasing type I errors, the method proposed by Miller and Siegmund was used.[34]

Calculation of GPS and mGPS: To calculate the GPS, one point was given for CRP >10 mg/L and/or albumin <35 g/L. For mGPS, one point for hypoalbuminemia was only awarded in the presence of elevated CRP levels (>10 mg/L), as previously described.[19]

Statistical analyses: Survival curves and analyses were calculated using the Kaplan-Meier and log-rank method, respectively. Hazard ratios to evaluate the impact of baseline characteristics to clinical outcome were calculated using the log-rank method. To adjust for factors associated with outcome, we performed a multivariate stratified cox model with the co-variables Log(CRP*fibrinogen/albumin), Log(Lc) and bone marrow blasts (all as numeric values) for each ELN risk group (favorable, intermediate and adverse).[33] Reported *P* values for baseline characteristics were from two-tailed Mann-Whitney or unpaired t-tests, and a value of $P<.05$ was considered significant. Analyses were conducted in GraphPad Prism version 7.0 (Graphpad Software, Inc., La Jolla, CA, USA) and R version 3.4.4 (R Foundation, Vienna, Austria).

Results

Patients: We identified 282 consecutive patients with newly diagnosed AML aged ≤65 years receiving at least one cycle of induction chemotherapy with complete data sets available for CRP, fibrinogen and albumin serum levels. All patients were at first diagnosis of AML before initiation of intensive induction treatment. We summarized the clinical characteristics of all patients in **Table 1**. Distribution of acute phase protein levels is shown in **Supplemental Figure 1.**

Comparison of disease characteristics in patients with high versus low CFA ratio: According to the method by Miller and Siegmund,[34] the optimal cutoff for the CFA ratio for stratification was determined at 3.06 for the survival rates, and patients were dichotomized into two cohorts accordingly (high CFA versus low CFA ratio). Hemoglobin and platelet level, age, gender, and FAB classification did not differ between both groups. ELN risk groups and individual cyto- and molecular genetic characteristics were similar with the exception of *FLT3*-ITD/*NPM*1 wild-type, which was more common within the higher CFA ratio group (10.7 vs. 1.2%, *P*<.001). The proportions of patients undergoing autologous or allogeneic stem cell transplantations were similar in the low and high CFA ratio cohorts (autologous SCT 38.2 vs. 33.6%, *P*=.455; allogeneic SCT 28.8 vs. 22.1%, *P*=.220). Differences were observed for peripheral leukocytes and blast counts at diagnosis, which both were higher in the high CFA ratio cohort (median leukocytes 46.9 vs. 25.2G/L, *P*=.009; median peripheral blasts 51.0 vs. 38.7%, *P*=.001; and median marrow blasts 71.4 vs. 62.3%, *P*=.003). We observed no differences in DIC rates in APL patients as defined by an ISTH DIC score of ≥5 between the high and low CFA ratio groups (83.3 vs. 78.6%, *P*>.999).

Clinical relevance of the novel CFA ratio: Survival data comparing high CFA versus low CFA ratio groups were summarized in **Figure 1** and **Table 2**. We observed that the median progression free survival in the low CFA ratio group was higher than in the high CFA ratio group (26.2 vs. 7.7 months; *P*<.001). Similarly, median disease-free (56.4 vs. 8.7 months; *P*<.001) and overall survival (61.2 vs. 13.8 months; *P*<.001) were longer in the low CFA ratio

group. Response to induction treatment was better in the low ratio group with CR rates of 89% vs. 76%, respectively (*P*=.006). When adjusting for potential confounders in a multivariate analysis including CFA ratio, peripheral leukocytes, and bone marrow blasts, results for progression free and overall survival remained significant (Adjusted HR 1.14 (1.05-1.25, *P*=.003); and 1.19 (1.08-1.31, *P*<.001; **Table 3**). Early mortality tended to be higher in the high CFA ratio group (9 vs. 6% after 1 month, *P*=.350; 20 vs. 11% after 3 months; *P*=.063), with this difference being significant 6 months after initiation of therapy (34 vs. 20%, *P*=.013).

Clinical impact of the (modified) Glasgow prognostic score and mGPS: Next, we investigated the prognostic relevance of the GPS and mGPS in AML patients. Results were summarized in **Supplemental Table 1**. Stratification of patients according to GPS indicated the best median PFS of 26.2 months for patients with GPS score 0, of 12.6 months for GPS score 1, and 9.0 months for GPS score 2 (*P*=.154). Similarly, the median DFS was 56.4 months (score 0), 16.8 months (score 1), and 13.2 months (score 2; *P*=.477). The median OS were 61.2 months, 24.0 months and 15.7 months, respectively (*P*=.082).

When patients were stratified according to mGPS, we observed a median PFS of 26.8 months (mGPS 0), 11.9 months (mGPS 1), and 9.0 months (mGPS 2, *P*=.051). The median DFS were 30.8 months, 14.2 months, and 13.2 months (*P*=.2512), and the median OS were 61.2 months, 21.2 months, and 15.7 months (*P*=.026). The difference was evident between mGPS score 0 and 1 patients, whereas survival curves between mGPS 1 and 2 appeared similar. Finally, when comparing patients with mGPS 0 to patients with combined mGPS 1 and 2, survival differences were significant (**Supplemental Figure 2**).

Discussion

In this retrospective, single-center analysis we aimed to investigate the prognostic significance of pretreatment acute phase protein levels on outcome in newly diagnosed AML patients undergoing intensive induction chemotherapy. We recently reported that elevated levels of fibrinogen are associated with adverse outcome in newly diagnosed AML patients.[27] Elevated levels of acute phase proteins as well as CRP/albumin ratio were linked to adverse outcome in various solid tumors as well as hematologic malignancies. To the best of our knowledge, this association so far has not been investigated in AML patients.

An elevated GPS has been shown to be associated with weight loss,[35–38] poor performance status[35] and reduced dietary intake[38] in patients with solid tumors. Moreover, the GPS has been shown to predict increased toxicity in patients undergoing chemotherapy.[39,40] In this study, we developed a novel score termed CFA ratio, which includes pretreatment CRP, fibrinogen, and albumin levels. When applying this novel score to a large cohort of AML patients undergoing intensive induction treatment, we observed that patients with higher CFA ratios had shorter progression-free, disease-free and overall survival as compared to patients with lower CFA ratios. In particular, a CFA ratio >3.06 was associated with adverse survival. Analyses for PFS and OS remained significant when adjusting for potential confounders in a multivariate analysis. Finally, patients with a higher CFA ratio also had lower CR rates. While early mortality tended to be higher in the high CFA ratio group, this was only significant after 6 months. A recent analysis showed a decrease in early mortality during induction therapy in AML patients from 2006 to 2016.[41] As our analysis includes patients treated between 2000 and 2018, comparison of early mortality may be biased by time period.

In a previous analysis, we found that AML patients with high versus low fibrinogen levels did not differ in the incidence of thromboembolic events or the frequency of bleeding.[23] Therefore, the integration of fibrinogen into the CFA ratio highlighted its relevance as an acute phase protein and to be independent in this large cohort from bleeding and coagulopathy as demonstrated by similar DIC rates between the two groups. In addition, we could demonstrate

that the original and the modified Glasgow prognostic score (GPS and mGPS), which have been verified in many solid tumor types, also has prognostic significance in AML patients. We found that AML patients with lower scores of the GPS and the mGPS had better survival rates. In particular, an mGPS score of 0 was associated with superior progression free, disease free and overall survival compared to scores ≥1. We did not directly compare the Glasgow prognostic score to our novel CFA ratio, however, the inclusion of Fibrinogen to the CRP/Albumin ratio led to enhanced statistical significance. Therefore, the CFA ratio can be considered as an easily applicable clinical score.

Inflammatory processes have been reported to play an important role in the proliferation of myeloid blasts.[42,43] Since cytokines influence signal transduction in hematopoietic cells, abnormal cytokine release through activity of inflammatory cells or leukemic precursor cells was reported to suppress apoptosis and differentiation of precursor cells leading to increased proliferation.[44] Anti-inflammatory cytokines such as TGF-ß inhibit proliferation of leukemic cells and control the expression of pro-inflammatory cytokines such as IL-1 or IL-6. Thus, downregulation of anti-inflammatory cytokines may lead to a predominance of pro-inflammatory and therefore pro-leukemic cytokines.[25] It can be postulated that an elevated CFA ratio or mGPS represents the underlying cytokine dysregulation. While it has been shown that levels of all IL-1, IL-6 and CRP are higher in cancer patients than in healthy controls, correlation of cytokines and acute phase protein levels is weak at best.[45,46] Therefore, it remains unclear whether adverse prognosis in AML patients with high CFA ratio is due to poor performance status and impaired tolerance of therapy or whether a higher ratio can be considered as hallmark of a more aggressive disease by a yet unknown mechanism.

Assessment of prognosis of AML patients mostly relies on pretreatment molecular and cytogenetic methods. While a number of driver mutations with known prognostic significance has been previously identified, novel mutations with yet unknown relation to disease progression or prognosis are currently discovered by next-generation sequencing (NGS) technique.[47] Novel approaches focus on post-treatment assessment of leukemic stem cell frequency by flow cytometry in combination with traditional flow minimal residual disease

(MRD) strategies, but this approach is so far only available in few laboratories.[48] Parameters such as fibrinogen, CRP and albumin on the other hand are routinely assessed and laboratory tests yield results within minutes. Therefore, scores based on acute phase proteins, such as the CFA ratio proposed in this work or the (m)GPS may provide an additional, rapidly available initial assessment of prognosis and risk upon diagnosis and may thereby contribute to patient information. During induction and consolidation treatment, the CFA score can offer a more differentiated mean of risk profiling and may lead to adaptation of surveillance strategies.

As our analysis is limited by its single-center, retrospective character, the CFA ratio may be independently validated by prospective multicenter approaches with validation cohorts. Due to missing data, a reliable statement about the performance status of patients in our analysis is not possible, however, all included patients were deemed fit for intensive treatment. Thus, collaborative leukemia study groups may investigate whether an increased CFA ratio and imbalances in acute phase reactants reflect an adverse performance status or whether they are a yet unknown surrogate marker for a more aggressive course of AML. As AML is a disease of the elderly and patients often present in a bad performance status unfit for intensive treatment, the CFA score could also be validated in a non-intensively treated cohort.

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Table 1: Patient and disease characteristics

Parameter	Low CFA ratio (n=160)	High CFA ratio (n=122)	*P*	s
Hemoglobin (g/L)	94.2 (±22.2)	91.8 (±22.5)	.373	ns
Leukocytes (G/L)	25.2 (±39.8)	46.9 (±74.2)	.009	**
Neutrophils (G/L)	3.2 (±7.7)	3.0 (±4.7)	.976	ns
Peripheral blasts (%)	38.7 (±31.3)	51.0 (±30.5)	.001	**
Bone marrow blasts (%)	62.3 (±26.1)	71.4 (±25.5)	.003	**
Platelets (G/L)	91.0 (±89.6)	82.4 (±84.0)	.337	ns
Gender, female/male	80/80 (50%/50%)	50/72 (41%/59%)	.149	ns
Age, years (range)	50.3 (19.3-65.9)	51.4 (19.9-65.8)	.441	ns
FAB Classification				
M0	20 (12%)	11 (9%)	.443	ns
M1	28 (18%)	22 (18%)	>.999	ns
M2	37 (23%)	28 (23%)	>.999	ns
M3	17 (11%)	8 (7%)	.292	ns
M4	26 (16%)	29 (24%)	.130	ns
M5	10 (6%)	9 (7%)	.812	ns
M6	5 (3%)	1 (1%)	.239	ns
M7	1 (1%)	4 (3%)	>.999	ns
unclassifiable	16 (10%)	10 (8%)	.681	ns
ELN risk stratification				
Favorable	61 (38%)	33 (27%)	.056	ns
m*NPM1* w/o *FLT3*-ITD	19 (12%)	12 (9%)	.702	ns
t(15;17)/*PML-RARA*	17 (11%)	8 (7%)	.233	ns
t(8;21)/*RUNX1-RUNX1T1*	12 (8%)	8 (7%)	.819	ns
inv(16)/*CBFB-MYH11*	7 (4%)	3 (2%)	.522	ns
CEBPA	6 (3%)	2 (2%)	.473	ns
Intermediate	66 (41%)	54 (44%)	.629	ns
NOS	49 (31%)	39 (33%)	.897	ns
m*NPM1* w/ *FLT3*-ITD	8 (5%)	10 (8%)	.329	ns
wt*NPM1* w/o *FLT3*-ITD	7 (4%)	4 (3%)	.762	ns
t(9;11)/*MLLT3-KMT2A*	2 (1%)	1 (1%)	>.999	ns
Adverse	33 (21%)	35 (29%)	.878	ns
Monosomy or complex	26 (16%)	16 (13%)	.503	ns
wt*NPM1* w/ *FLT3*-ITD	2 (1%)	13 (11%)	<.001	***
inv(3)/*EVI1* rearranged	4 (3%)	3 (2%)	>.999	ns
t(v;11)/*KMT2A* rearranged	1 (1%)	2 (2%)	.580	ns
t(6;9)/*DEK-NUP214*	0 (0%)	1 (1%)	.433	ns

Laboratory analyses and age indicated as median values. Plus/minus values indicate standard deviation of the mean. ELN: European LeukemiaNet; m: mutated; w/o: without; w/: with; NOS: not otherwise specified; wt: wild-type,

Table 2: Outcome				
	Low CFA ratio (n=160)	**High CFA ratio (n=122)**	***P***	**s**
Survival				
Progression free survival, months	26.2	7.7	<.001	***
Disease free survival, months	56.4	8.7	<.001	***
Overall survival, months	61.2	13.8	<.001	***
Follow up, months	56.2	54.7	-	-
Time to relapse, months	7.3	5.0	.135	ns
Response to therapy				
CR achieved, n (%)	142 (89%)	93 (76%)	.006	**
Relapse, n (%)	57 (36%)	49 (40%)	.458	ns
Mortality within 1 month, n (%)	9 (6%)	11 (9%)	.350	ns
Mortality within 3 months, n (%)	18 (11%)	24 (20%)	.063	ns
Mortality within 6 months, n (%)	32 (20%)	41 (34%)	.013	*
Mortality total, n (%)	74 (46%)	83 (68%)	<.001	***
Death in CR1, n (%)	9 (6%)	12 (13%)	.103	ns
Stem cell transplant				
Autologous, n (%)	61 (38%)	41 (34%)	.455	ns
Allogeneic, n (%)	46 (29%)	27 (22%)	.220	ns

Survival rates indicated as median values; CR: complete remission; Death in CR1 indicated as percentage of patients who achieved a complete remission; ns: not significant; * significant; CFA: CRP/fibrinogen/albumin ratio.

Table 3: Multivariate outcome analysis.

Parameter	C Index	Unadjusted HR (95%CI)	p	Adjusted HR (95%CI)	p
PFS	**0.621**	**1.8 (1.3-2.5)**	**.003**	**1.14 (1.05-1.25)**	**.003**
Log(CRP*Fib/Alb)		1.14 (1.05-1.25)	.003	-	-
Log(Lc)		1.18 (1.07-1.31)	.001	-	-
Bone marrow blasts		0.99 (0.99-1.00)	.006	-	-
DFS	**0.633**	**1.8 (1.3-2.5)**	**.028**	**1.10 (0.99-1.22)**	**.067**
Log(CRP*Fib/Alb)		1.10 (0.99-1.22)	.067	-	-
Log(Lc)		1.23 (1.09-1.38)	.001	-	-
Bone marrow blasts		0.99 (0.99-1.00)	.026	-	-
OS	**0.623**	**1.9 (1.4-2.7)**	**.001**	**1.19 (1.08-1.31)**	**<.001**
Log(CRP*Fib/Alb)		1.19 (1.08-1.31)	<.001	-	-
Log(Lc)		1.13 (1.02-1.26)	.018	-	-
Bone marrow blasts		0.99 (0.99-1.00)	.002	-	-

Stratified Cox model, with covariables Log(CRP*Fib/Alb), Log(Lc) and bone marrow blasts (as continuous variables) for each ELN risk class (favorable, intermediate, adverse). HR: hazard ratio; PFS: progression free survival; DFS: disease free survival; OS: overall survival; CRP: C-reactive protein; Fib: fibrinogen; Alb: albumin; Lc: leukocytes.

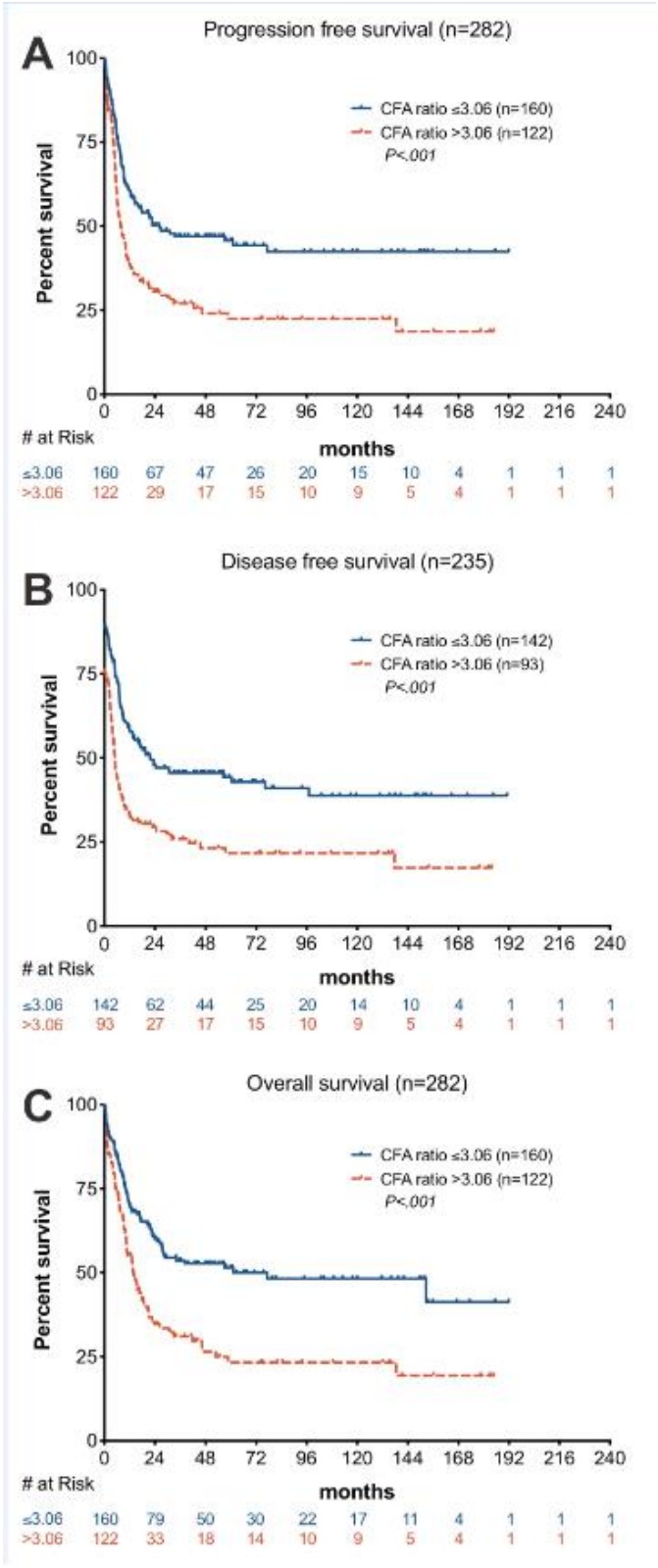

Figure 1: Survival according to the CFA (CRP*Fibrinogen/Albumin) ratio. Kaplan-Meier curves for progression free (**A**), disease free (**B**) and overall survival (**C**) according to CFA ratio.