Relationship between C-reactive Protein/Albumin Ratio and Subclinical Inflammation in Patients with Familial Mediterranean Fever

Korrelation zwischen C-reaktiven Protein/Albumin-Quotienten und subklinischen Entzündungen bei Patienten mit Familiärem Mittelmeerfieber

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Key words

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Schlüsselwörter

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ABSTRACT

Background Familial Mediterranean Fever (FMF), which is characterised by recurrent episodes of fever with serositis, is associated with ongoing inflammation without clinical findings during attack-free periods, leading to amyloidosis, the most important complication of FMF. The objective of this study was to investigate the C-reactive protein/albumin ratio (CAR) as a marker to identify subclinical inflammation in symptom-free FMF children and compare the CAR with other systemic inflammatory markers such as mean platelet volume (MPV), red cell distribution width (RDW), neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR).

Material and Methods We included 100 patients and 70 healthy subjects. Hospital records were obtained to collect data on laboratory findings and genetic mutations.

Results We found that the CAR levels of our FMF patients were significantly higher than those of the control group. We also evaluated that the CAR values had a higher area-under-the-curve value than the other systemic inflammation parameters including CRP, MPV, RDW, NLR, PLR based on Receiver-Operating Characteristics (ROC) analysis.

Conclusion It is important to identify subclinical inflammation in FMF patients with simple, reliable, easily accessible markers to avoid amyloidosis. Although the CAR might be used to assess subclinical inflammation in paediatric FMF patients, the prognostic value of CAR is not superior to CRP. Merging CRP and albumin into a single index thus provides no additional benefit in detecting subclinical inflammation in FMF.

ZUSAMMENFASSUNG

Hintergrund Das familiäre Mittelmeerfieber (FMF), gekennzeichnet durch wiederkehrende Fieberschübe mit Serositis, weist im anfallsfreien Intervall kontinuierliche Entzündungen ohne klinische Befunde auf und führt zu Amyloidose, der Hauptkomplikation von FMF. Ziel dieser Studie war die Untersuchung des C-reaktiven Proteins/Albumin-Quotienten (CAR) als Marker zur Identifizierung subklinischer Entzündungen bei Kindern ohne FMF-Symptome und der Vergleich des CAR mit den anderen identifizierten Entzündungsmarkern wie mittleres Thrombozytenvolumen (MPV), Erythrozytenbreitenverteilung (RDW), Neutrophilen/Lymphozyten-Verhältnis (NLR) und Thrombozyten/Lymphozyten-Verhältnis (PLR).

Testmaterial und -methoden Wir bezogen 100 Patienten und 70 gesunde Probanden ein. Krankenhausdaten wurden erstellt,

um Daten über Laborbefunde und genetische Mutationen zu sammeln.

Ergebnisse Wir stellten fest, dass die CAR-Werte unserer FMF-Patienten signifikant höher waren als die der Kontrollgruppe. Wir bewerteten auch, dass die CAR-Werte eine höhere Fläche unter dem Kurvenwert hatten als die anderen systemischen Entzündungsparameter, einschließlich CRP, MPV, RDW, NLR, PLR, basierend auf der ROC-Analyse (Receiver-Operating Characteristics).

Schlussfolgerung Es ist wichtig, subklinische Entzündungen bei FMF-Patienten mit einfachen, zuverlässigen, leicht zugänglichen Markern zu identifizieren, um Amyloidose zu vermeiden. Obwohl CAR zur Beurteilung subklinischer Entzündungen bei pädiatrischen FMF-Patienten eingesetzt werden könnte, ist der prognostische Wert des CAR dem CRP nicht überlegen. Die Kombination von CRP und Albumin zu einem einzigen Index bietet daher keinen zusätzlichen Vorteil bei der Erkennung subklinischer Entzündungen bei FMF.

Introduction

Familial Mediterranean Fever (FMF) is an autoinflammatory condition inherited autosomal recessively and described as recurrent, self-limiting attacks of fever and synovitis, peritonitis and pleuritis [1, 2]. FMF varies according to different ethnic groups, being frequently seen in Jews, Turks, Arabs, and Armenians [3]. The gene encoding the pyrin/marenostrin proteins located on chromosome 16p, regulates fibroblasts and leukocytes inflammation and apoptosis cascade and encodes the Mediterranean fever gene (MEFV) [4]. The rate of MEFV gene mutation is reported as 1/5 in Turks, Jews and Arabs, and 1/7 in Armenians [5]. Mutations in the MEFV gene initiate an uninterrupted inflammatory cascade [6]. Inflammatory mediators, such as tumour necrosis factor alpha (TNF- α), interleukin-6 (IL-6), IL-8, and IL-10 have been evaluated to be elevated during attacks and attack-free intervals of FMF [7, 8]. Acute phase reactants, such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, and serum amyloid A (SAA) also increase during attack periods but return normal during attack-free intervals [9]. In some patients, subclinical inflammation (SI) may progress during attack-free intervals in FMF and triggers amyloidosis despite colchicine therapy [10, 11]. Recently, inflammation during the symptom-free periods of FMF has been reported to correlate with simple inflammatory-based scores, including the mean platelet volume (MPV), red cell width distribution (RDW), neutrophil/lymphocyte ratio (NLR), and platelet/lymphocyte ratio (PLR) [12–16]. The CRP/serum albumin ratio (CAR) is a new inflammation score used as a marker of chronic inflammation and prognosis in solid tumours [17], critically ill patients [18], rheumatoid arthritis [19], and ANCA-associated vasculitis [20]. The current study aimed to assess CAR levels as a marker of SI during the attack-free period in FMF patients. We also compared the CAR levels with the NLR, PLR, RDW and MPV values between the patients with and without SI.

Material and Methods

We retrospectively evaluated 100 patients with FMF that presented to the Paediatric Nephrology and Rheumatology Department of Manisa Celal Bayar University School of Medicine between June 2010 and June 2020. All patients were diagnosed with FMF according to the Tel-Hashomer criteria [21] and included in regular colchicine therapy. As the control group, we obtained the medical records of 70 healthy age- and sex-matched children referred to our outpatient clinic without any inflammatory manifestation. Patients with any infection, acute or chronic inflammatory or other chronic disease, malnutrition, or failure to thrive that might cause hypoalbuminemia and those without drug compliance were excluded from the study. The study was approved by the local ethics committee. Written informed consent was obtained from all participants.

The demographic, clinical and laboratory parameters including a complete blood cell count (CBC) analysis, biochemical data, and genetic findings were retrospectively obtained from the hospital records of the patients during the attack-free period when the patients were symptom-free. SI was defined as the elevation of at least one acute phase reactant during an attack-free period [22]. NLR, PLR, MPV, RDW and CAR were derived from the CBC analysis.

Genetic

A genetic analysis was routinely performed when FMF was diagnosed. DNA was obtained using the QIAamp DNA blood isolation kit (Qiagen GmbH) following the manufacturer's instructions using 2 mL of peripheral blood that had been gathered into ethylenediaminetetraacetic acid-anticoagulated tubes with the regular venepuncture method. A Thermo Scientific NanoDrop spectro-photometer was used to determine the DNA concentration. The profiles of the 22 most common pathogenic MEFV gene variants (E148Q, P369S, H478Y, F479L, S675N, G678E, M680I (G > C), M680I (G > A), M680L, T681I, I692del, M694V, M694I, M694L, K695R, K695M, R717S, I720M, V722M, V726A, A744S, and R761H) were genotyped by pyrosequencing (Qiagen, Germany).

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) for Windows, v. 22 (IBM SPSS Inc. Chicago, USA) was used for statistical analyses. Quantitative variables were expressed as mean ± standard deviation (SD) or median as appropriate while categorical variables were obtained as percentages. Student's t-test or the Mann-Whitney U test was conducted to evaluate the differences between the groups in terms of continuous variables. The $\chi 2$-test was used to evaluate the categorical variables. The Spearman correlation was performed to evaluate the relationship between the variables. A two-tailed p value of < 0.05 was considered as statistically significant. Pairwise comparison of area under ROC curves was conducted using DeLong's test by MedCalc statistical software ((version 11.3.8.0, Mariakerke, Belgium).

▶ **Table 1** Demographic characteristics and laboratory findings of the FMF and control groups.

Characteristics	FMF group (n = 100)	Control group (n = 70)	P-value
Age (years)	12.7 ± 4	12.09 ± 3.41	0.313
Sex (F/M)	42/58	37/33	0.164
Family history of FMF (%)	61 (%35.9)	10 (%14.2)	**<0.001**
CRP (mg/dL)	0.8 ± 1.4	0.28 ± 0.17	**0.002**
Albumin (g/dL)	4.11 ± 0.58	4.34 ± 0.26	**0.003**
Lymphocytes (10^3/μL)	3.10 ± 2.1	3.762 ± 2.23	0.06
Platelets (10^3/μL)	332 ± 97	339 ± 84	0.62
MPV (fL)	8.5 ± 1.2	8.5 ± 0.9	0.97
RDW (%)	14.57 ± 2	15.6 ± 14.4	0.48
CAR	0.21 ± 0.41	0.06 ± 0.05	**0.003**
NLR	2.53 ± 38	1.5 ± 1	**0.038**
PLR	134.6 ± 91.3	110.6 ± 48.3	**0.046**

F: female, M: male, FMF: familial Mediterranean fever, CRP: C-reactive protein, MPV: mean platelet volume, RDW: red cell width distribution, CAR: C-reactive protein/serum albumin ratio, NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio.

Results

The demographic characteristics and laboratory data of the FMF and control groups are presented in ▶ **Table 1**. The mean age of the FMF patients was 12.7 ± 4 years and that of the control group was 12.09 ± 3.41 years. The female/male ratio was 42/58 for the patients with FMF and 37/33 for the control group. There was no significant difference between the FMF patients and the control group in terms of age and gender (p = 0.31 and p = 0.164, respectively). The mean follow-up duration was 5.29 ± 2.9 years. The CRP levels were 0.8 ± 1.4 mg/dl for the FMF patients during the attack-free period and 0.28 ± 0.17 mg/dl in the control group, indicating significantly higher values in the patient group (p = 0.002). The mean value of albumin, a negative acute phase reactant, was significantly lower in FMF patients (4.11 ± 0.58 g/dL) compared to the control group (4.34 ± 0.26) (p = 0.003). The CAR levels were 0.21 ± 0.41 for the FMF group and 0.06 ± 0.05 for the control group, being significantly higher in the former (p = 0.003). The NLR levels were also significantly higher in the patients with FMF (2.53 ± 3.8) compared to the controls (1.5 ± 1) (p = 0.038). The PLR levels were 134.6 ± 91.3 in the FMF patients and 110.6 ± 48.3 in the control group, indicating significantly higher values in the FMF patients (p = 0.046). No significant difference was found between the attack-free FMF patients and the control group in terms of the lymphocytes, platelets, MPV and RDW (p = 0.06, p = 0.62, p = 0.97, p = 0.48, respectively).

The FMF patients were categorised into two groups according to the association of SI defined as the elevation of at least one acute phase reactant during an attack-free period. There were 29 patients with high CRP (> 0.5 mg/dl), 25 with high ESR (> 8 mm/hr), and 13 with high fibrinogen (> 393 mg/dl). Thirty-nine patients had SI. The demographic characteristics, laboratory findings and PRAS disease severity scores of the patients with and without SI are shown in ▶ **Table 2**. There was no significant difference between the FMF patients with and without SI according to age, gender, consanguinity, symptoms (e. g., fever, abdominal pain, chest pain, and arthritis), PRAS disease severity score, lymphocytes, NLR, PLT, and PLR (p = 0.52, p = 0.57, p = 0.11, p = 0.84, p = 0.22, p = 0.75, p = 0.51, p = 0.28, p = 0.75, p = 0.067, p = 0.95, p = 0.24, respectively). A family history of FMF, ESR, fibrinogen, CRP, albumin, CAR, and neutrophil count were significantly higher in FMF patients with SI than those without SI (p = 0.004, p < 0.001, p = 0.001, p < 0.001, p < 0.001, p < 0.001, p = 0.015, respectively).

▶ **Table 2** Comparison of the participants with and without SI.

Characteristics	FMF with SI (n : 39)	FMF without SI (n : 61)	P-value
Age onset of disease (years)	5.94 ± 3	6.31 ± 3.2	0.57
Sex (F/M)	15/24	27/34	0.57
Consanguinity (%)	4/39(10.25%)	14/61(23%)	0.11
Fever (%)	38/39	59/61	0.84
Abdominal pain (%)	31/39	54/61	0.221
Chest pain (%)	4/39	6/61	0.75
Arthritis (%)	16/39	21/61	0.51
Family history of FMF (%)	17/39	44/61	**0.004**
PRAS	8.1 ± 1.9	7.61 ± 1.9	0.24
ESR (mm/hr)	15.23 ± 10.47	5.46 ± 1.65	**<0.001**
Fibrinogen (mg/dL)	299 ± 95	245.6 ± 68.8	**0.001**
CRP (mg/dL)	1.64 ± 2.04	0.25 ± 0.16	**<0.001**
Albumin (g/dL)	3.8 ± 0.6	4.23 ± 0.45	**<0.001**
CAR	0.45 ± 0.59	0.06 ± 0.056	**<0.001**
Neutrophil (× 10^3)	6.3 ± 3.37	4.9 ± 2.5	**0.015**
Lymphocytes (× 10^3)	3.2 ± 3	3.06 ± 1.5	0.75
NLR	3.4 ± 5.6	1.97 ± 1.7	0.067
Platelets (× 10^3)	333 ± 93	332 ± 100	0.95
PLR	147 ± 130	126 ± 56	0.245

SI: subclinical inflammation, F: female, M: male, FMF: familial Mediterranean fever, PRAS: disease severity score, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, RDW: red cell width distribution, CAR: C-reactive protein/serum albumin ratio, NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio.

The FMF patients were also categorised according to their MEFV gene mutations. The distribution of the MEFV mutations of the patients was as follows: 37 cases (37 %) had two mutations in the MEFV gene [23 homozygous (M694V, n = 19) and 14 (14 %) compound heterozygous], 48 patients (48 %) were heterozygous [18 had M694V, 13 had E148Q, 8 had V726A, 3 had M680I ,3 had R761H, 2 had R202Q, 1 had A744S] and 12 patients (12 %) had no mutation. The M694V homozygous (n = 19) and M694V heterozygous (n = 33) cases and the patients with no M694V mutation (n = 48) were compared with regard to their demographic characteristics and laboratory findings (▶ **Table 3**). SI was significantly higher in patients with M694V mutations (p = 0.025). However, there

▶ **Table 3** Comparison of M694V homozygous, M694Vheterozygous and no M694V mutation patients.

Characteristics	M694Vhomozygous (n:20)	M694Vheterozygous (n:32)	No M694V mutation (n:48)	P-value
Age onset of disease (Years)	5.9±3.5	6.23±3	6.25±3.1	0.89
Sex (F/M)	12/8	11/21	19/29	0.174
Consanguinity (%)	5/20 (25%)	4/32 (12.5%)	9/48(18.75%)	0.51
Fever (%)	20/20(100%)	31/32(96.9%)	46/48(95.8%)	0.66
Abdominal pain (%)	16/20(80%)	29/32(90%)	40/48(83%)	0.53
Chest pain (%)	1/20(5.5%)	4/32(12.5%)	9/48(18.8%)	0.32
Arthritis (%)	7/20(33%)	11/32(34%)	19/48(39.6%)	0.88
Family history of FMF (%)	14/20(66%)	18/32(56%)	29/48(60%)	0.62
PRAS	8.1±1.92	7.47±1.9	7.6±2.14	0.48
SI (%)	12 (60%)	16 (50%)	11 (23%)	**0.005**
ESR (mm/hr)	9.65±6.6	11.78±10.1	7.44±6.8	0.063
Fibrinogen (mg/dl)	285±81.6	264±82	260±86	0.521
CRP (mg/dL)	1.5±2.7	0.78±0.81	0.51±0.8	0.035
Albumin (g/dL)	3.97±0.65	4±0.55	4.2±0.56	0.24
CAR	0.41±0.8	0.2±0.21	0.14±0.24	0.047
Neutrophil ($\times 10^3$)	6.4±2.9	4.8±2.3	4.8±2.0	0.027
Lymphocytes ($\times 10^3$)	2.63±1.2	3.6±3.4	2.94±1.2	0.199
NLR	2.9±1.7	1.9±2	1.9±1.24	0.063
Platelets ($\times 10^3$)	326±72	318±103	344±102	0.493
PLR	168±167	116±61	133±55	0.135

F: Female, M: Male, FMF: Familial Mediterranean Fever, PRAS: disease severity score, SI: subclinical inflammation, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, CAR: C-reactive protein/serum albumin ratio, NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio.

was no significant difference between these three groups in terms of age, gender, consanguinity, FMF symptoms, family history of FMF, PRAS score, and laboratory parameters (ESR, fibrinogen, CRP, albumin, CAR, and neutrophil, lymphocyte and platelet counts).

According to the receiver operating characteristics (ROC) analysis, CAR had an area under the curve value of 0.928 (95%CI, 0.879–0.977) and was determined to be a reliable marker for SI in FMF patients. CAR had a slightly higher AUC value than CRP (0.916, 95%CI, 0.863–0.972). CAR had a higher AUC value than the other systemic inflammation parameters, including albumin, ESR, fibrinogen, RDW, NLR, PLR with AUC values of 0.727, 0.822, 0.664, 0.629, 0.598, 0.541, respectively. After pairwise comparison of AUC values, we found no significant difference between AUC of CAR and CRP (AUC:0.928; 95%CI: 0.879–0.977, z=0.75, p=0.45), there was significant difference between CAR and albumin levels (AUC: 0.928; 95%CI: 0.879–0.977vs AUC: 0.727; %95CI: 0,629–0,811; z= 3.6, p= 0,003).

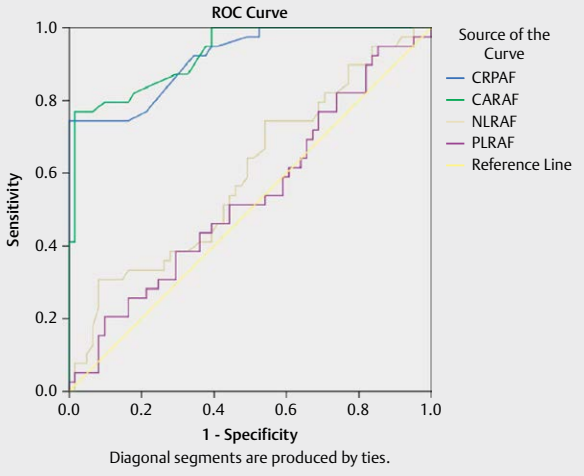
Discussion

Although FMF is characterized by self-limiting, remitting relapsing 24- to 72-hour episodes of fever with serositis involving the pleura, peritoneum and joints with elevations in serum inflammatory markers, acute phase reactants can remain high in nearly half of the patients even during the attack-free period [11, 22]. Our results indicate that 39% of our patients had SI defined as an increased level of at least one acute phase reactant. In previous studies, the rate of SI was determined as 63% by Korkmaz et al. [23] and 31.4% by Çakmak et al [24]. SI may lead to impairment in quality of life, growth retardation, normocytic normochromic anaemia, predisposition to atherosclerosis and coronary heart disease, female infertility, depression, and amyloidosis [10]. Amyloidosis is the most important and devastating complication of FMF [25]. Our patients did not have amyloidosis or severe proteinuria. The development of SI despite colchicine therapy may work as a contributor to the main pathogenesis of amyloidosis [11, 14]. To date, some inflammatory markers have been studied to determine their ability to predict SI in FMF [11–16]. Duzova et al. defined SAA as a useful marker to assess SI [11]. Ahsen et al. found that the NLR values were significantly higher in patients with SI and in FMF patients with M694V mutations [12]. Sakallı et al. suggested that higher MPV values, especially in with FMF patients with proteinuria might be a critical determinant of SI and amyloidosis [13]. Ozer et al. found that the PLR, NLR, MPV and RDW levels could be used to determine SI, and NLR had the strongest correlation with SI and amyloidosis [14]. Although we determined higher AUC values for NLR in the ROC analysis compared to the PLR and MPV levels, NLR in our hands failed to significantly discriminate between SI and Non-SI, in accordance with Basaran et al. who reported that neither NLR nor MPV was useful in detecting SI but they were

▶ **Table 4** Receiver operating characteristics analysis for subclinical inflammation.

Test Result Variable(s)	Area Under the Curve	P-value	95 % Confidence Interval	
			Lower Bound	Upper Bound
CARAF	0.928	**<0.001**	0.879	0.977
CRPAF	0.917	**<0.001**	0.863	0.972
Albumin	0.727	**<0.001**	0.629	0.811
ESR	0.822	**<0.001**	0.725	0.918
Fibrinogen	0.664	**0.006**	0.549	0.779
RDWAF	0.629	**0.031**	0.515	0.742
NLRAF	0.598	0.102	0.483	0.712
PLRAF	0.541	0.492	0.424	0.658
MPVAF	0.517	0.772	0.402	0.633

CRP: C-reactive protein, AF: Attack-free, CAR: C-reactive protein/serum albumin ratio, NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio, MPV: mean platelet volume, ESR: erythrocyte sedimentation rate.



▶ **Fig. 1** Receiver- operating characteristics (ROC) curve for CAR for subclinical inflammation in attack free FMF patients.

significant in comparing inflammation between the FMF group and the control group [15]. Marzouk et al. suggested that RDW and ESR could be used as indicators of SI in children with FMF [16]. In our study, we aimed to demonstrate the relationship between CAR and SI and identified the best marker for SI in this patient group by comparing their CAR, RDW, NLR, PLR and MPV values. Our results revealed that CRP and CAR had the strongest association with SI in children with FMF. But replacing CRP by CAR in the assessment of SI gives no additional benefit. We also observed that ESR and fibrinogen could be useful to determine SI but they have no better contribution than CRP and CAR (▶ **Fig. 1**)(▶ **Table 4**).

We also investigated SI in patients with M694V homozygous and heterozygous mutations and those with no M694V mutation, considering that M694V mutations are correlated with SI and amyloidosis. We found that SI was significantly higher in homozygous and heterozygous patients with M694V mutations in accordance with previous findings [12, 26]. However, we did not obtain any significant difference in SI between the M694V homozygous or M694V heterozygous cases (p = 0.5).

CRP is an acute phase reactant produced by hepatocytes during inflammation however, many studies have shown that CRP is also associated with chronic inflammation [27]. Albumin, the most abundant protein of blood plasma, is a negative acute phase reactant showing inflammation and oxidative stress [28]. The measurement of CRP and albumin levels is an easy, inexpensive and simple method compared to the analysis of inflammatory cytokines, including IL-1β, IL-6, IL-8, and TNF-α or SAA for FMF patients. CAR is widely used to predict the patient's outcome in many types of cancer [17], critically ill patients [18], vasculitis [20], Crohn's disease [29], sepsis [30], and moreover it was reported to perform better than CRP alone [8, 30]. In one of the first studies investigating the role of CAR in rheumatologic disease, Seringec Akkececi et al. found that CAR was correlated with disease activity in Takayasu arteritis [31]. Yang et al. reported that the CAR and the albumin/fibrinogen ratio could serve as inflammatory markers for monitoring disease activity in rheumatoid arthritis [19].

The strengths of our study are that we had a high number of patients with SI (39 %), which allowed us to compare their data to those with no subclinical inflammation. We also compared the findings according to the presence of M694V mutations in the FMF attack-free group. Neither analysis revealed statistical differences in markers, namely CAR, CRP, NLR, and PLR. Furthermore, considering that lymphocyte and neutrophil counts vary in children with age, we included patients of similar age in the sample. Nevertheless, there were also certain limitations to our study; e. g., the retrospective single-centre design and the small sample size. We also did not study the IL-1β, IL-6, IL-8, TNF-α or SAA levels in our patients.

Conclusion

To our best knowledge, this is the first study showing the relationship between CAR and SI in FMF patients. A higher CAR level indicates a higher inflammatory state and seems to be as accurate as CRP in detecting SI based on the ROC curve analysis. However, the prognostic value of CAR is not superior to CRP. Thus, merging CRP and albumin in a single index provides no additional benefit in detecting SI in FMF.

Conflict of Interest

The authors declare that they have no conflict of interest.

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