Implications of fever on erythrocyte sedimentation rate but not on C-reactive protein concentrations at the time of diagnosis of polymyalgia rheumatica. Comments on Betrains *et al*.

Sirs,

We read with interest the letter recently accepted for publication in *Clinical and Experimental Rheumatology*, where Betrains *et al*. (1) reported an age- and sex-matched monocentric case-control study regarding clinical implications of fever at diagnosis in patients with polymyalgia rheumatica (PMR). Constitutional manifestations including fever are cardinal signs of PMR. Interestingly, Betrains *et al*. did not find any significant correlation between fever and median C-reactive protein (CRP) concentrations (p=0.09) whereas significantly higher (p=0.004) erythrocyte sedimentation rate (ESR) levels were present in PMR patients with fever.

To re-evaluate these surprising results, we assessed all patients with newly diagnosed PMR from a local registry (followed at the rheumatology clinic of the Pomeranian Medical University in Szczecin, Poland; research approved by the decision KB-0012/111/10 and KB-0012/12/14 of local ethical committee) of the period 2006-2020. Giant cell arteritis (GCA) was excluded on the basis of presence of signs or symptoms of GCA, routine ultrasound examination of temporal, axillary, subclavian and carotid arteries (by experienced ultrasonographists), contrasted aortic CT (in 81 patients), rarely PET imaging. Finally, a follow-up of at least one year was required in order to exclude possible diagnostic changes.

Out of 222 PMR patients, we excluded 52 due to missing data on fever, ESR or CRP, and 94 because of concomitant/overlapping vasculitis. Therefore, we assessed 86 patients with isolated PMR. Among the 53 PMR patients with normal body temperature, we then excluded 13 due to match for age and sex, and due to relevant co-morbidities. Finally, we divided the enrolled 73 patients into three groups: group A ≤37.2°C, 40 patients; group B = low-grade body temperature elevation (>37.2 <38°C), 13 patients; group C = fever (≥38°C), 20 patients.

When ESR and CRP were compared with body temperature, we found that ESR levels were significantly higher in fever group (normal temperature: 66.83±28.64; low-grade body temperature elevation: 64.15±29.58; fever 88.60±72.32, p=0.017) whereas CRP concentrations had no statistically significant difference in the three groups. Univariate and stepwise multivariate analysis (gender as excluded variable) confirmed that only ESR was significantly associated with fever (Table I).

Table I. Erythrocyte sedimentation rate and C-reactive protein concentrations according to body temperture class at the time of diagnosis of polymyalgia rheumatica. ANOVA.

	All (n=73)	Normal temperature <37.2 °C (n=40)	Low-grade body temperature elevation ≥37.2°C BT <38°C (n=13)	Fever ≥38°C (n=20)	*p*
Age at diagnosis, years	68.60±8.37	68.95±9.18	67.69±7.60	68.85±7.44	NS
Female, %	75.3%	77.5%	76.9%	70%	NS
CRP, mg/L	46.73±40.79	45.70±42.75	42.760±33.27	51.46±42.47	NS
ESR, mm/h	72.31±30.59	66.83±28.64	64.15±29.58	88.60±72.32	0,017
Haemoglobin, g/dL	11.99±1.41	12.25±1.26	12.32±1.27	11.29±1.57	0,030

Data expressed as mean±standard deviation or percentual.

CRP and ESR values and body temperature class. Student's t-test.

	Normal temperature *vs*. low grade fever	Normal temperature *vs*. fever	Low grade fever *vs*. fever
CRP	45.70±42.75 *vs*. 42.7 60±33.27 *p*=ns	45.70±42.75 *vs*. 51.46±42.47 *p*=ns	42.760±33.27 *vs*. 51.46±42.47 *p*=ns
ESR	66.83±28.64 *vs*. 64.15±29.58 *p*=ns	66.83±28.64 *vs*. 88.60±72.32 *p*=ns	64.15±29.58 *vs*. 88.60±72.32 *p*=ns

Univariate analysis of body temperature class and different covariates in all enrolled patients.

Body temperature class	r	*p*
ESR	0.284	0.015

r: coefficient of variation; *p*: Pearson's coefficient,

Stepwise multivariate analysis: body temperature class and different covariates in all enrolled patients. Gender as excluded variable.

Body temperature class	β	*p*
ESR	2.405	0.019

β: coefficient of regression.

Our data surprisingly confirmed that of Betrains *et al*.: there was fever implication on ESR but not of CRP in the patients at the time of diagnosis of PMR. Study limitations that should be listed where the same as in the study by Betrains *et al*.

In PMR patients, fever and other constitutional manifestations are considered to be provoked by systemic inflammation induced by some cytokines. Interleukin 6 and 1 are the most relevant ones, and are strongly associated with increase of CRP concentration (2). CRP might have been be preferred in some sites after it was demonstrated a more sensitive marker than ESR for biopsy-proven GCA (3). Our patients did not reach significant correlation with CRP and body temperature.

Could the small cohort size of our cohort be a cause? However, why does ESR and CRP significance differ? Are there other fever related factors in PMR that influence ESR more than CRP? More studies seem needed to explain this phenomenon.

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References

1. BETRAINS A, BOECKXSTAENS L, VAN LAERE K, VANDERSCHUEREN S, BLOCKMANS D: Clinical implications of fever at diagnosis in polymyalgia rheumatica: an age- and sex-matched case control study of 120 patients. *Clin Exp Rheumatol* 2021 Jul 24; Online ahead of print PMID 34369355.
2. DEJACO C, DUFTNER C, BUTTGEREIT F, MATTESON EL, DASGUPTA B: The spectrum of giant cell arteritis and polymyalgia rheumatica: revisiting the concept of the disease. *Rheumatology* (Oxford) 2017; 56: 506-15.
3. KERMANI TA, SCHMIDT J, CROWSON CS *et al*.: Utility of erythrocyte sedimentation rate and C-reactive protein for the diagnosis of giant cell arteritis. *Semin Arthritis Rheum* 2012; 41: 866-71.