Clinical implications of fever at diagnosis in polymyalgia rheumatica: an age- and sex-matched case control study of 120 patients. Reply to Milchert *et al*. and Manzo *et al*.

Sirs,

We would like to thank Milchert *et al*. for their reply to our recent study on polymyalgia rheumatica (PMR) patients with fever (1, 2). We are pleased to learn that the authors confirmed that erythrocyte sedimentation rate (ESR) but not CRP is associated with fever in patients with PMR.

While CRP and ESR both increase due to an acute phase response, ESR may be considered as a non-specific marker that is also susceptible to changes in other serum proteins and discordant results are common (3, 4). Chronic inflammation may result in several laboratory abnormalities, including anaemia, hypoalbuminaemia, and hypergammaglobulinaemia, all of which may also influence the ESR (5-7). Patients with fever had a significantly longer delay-to-diagnosis compared to patients without fever in our study (median [Q1-Q3], 7.5 [4–16] weeks *vs*. 4 [3–8] weeks; p=0.004). While we do not have laboratory data available to confirm this suspicion, we assume alterations in the aforementioned proteins may explain why ESR is significantly associated with fever in patients with PMR and CRP is not. Thus, the significant association between ESR and fever, which was also confirmed by Milchert *et al*., may be explained by the longer disease duration which was observed in PMR patients with fever.

We would also like to thank Manzo *et al*. for their interesting reply (8). Our findings seem to confirm that fever may be a confounding factor influencing diagnostic delay in patients with PMR, as reported by Manzo *et al*. (9). As we wanted to evaluate fever related to PMR, we excluded patients who had alternative causes of fever at presentation, including malignancies. While the presence of fever often makes physicians think about infection, we do agree that it is important to consider malignancy in patients presenting with PMR-like manifestations (10). In our centre, malignancy is often detected early in patients with a PMR-like presentation by means of diagnostic positron emission tomography imaging. Therefore, malignancy would not explain fever in the patients with PMR that were reported, but referral bias may indeed account for differences between university hospitals and primary care practice.

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