## Serum aldolase serves as a useful marker for diagnosis and assessment of disease activity in patients with adult-onset Still's disease

Sirs,

Adult-onset Still's disease (AOSD) has non-specific symptoms and laboratory findings; its diagnosis and accurate determination of disease activity are difficult. Although factors predictive of AOSD, and the clinical manifestations thereof, have been reported (1, 2), useful biomarkers are required in addition to those used for other rheumatic diseases (3, 4). Two studies reported that serum aldolase levels were increased in AOSD patients (5, 6). However, no study has yet explored the precise relationship between AOSD status and serum aldolase level. Here we assessed the utility of serum aldolase as a biomarker for the diagnosis and activity of AOSD.

We collected blood samples and symptoms from AOSD (n=15), rheumatoid arthritis (RA; n=30), Sjögren's syndrome (SS; n=35), systemic lupus erythematosus (SLE; n=30) and systemic sclerosis (SSc; n=12) patients. AOSD patients were diagnosed using the criteria of Yamaguchi *et al*. (1992). Of the 15 patients, 12 (80%) were female; the median disease duration was 2.53 (0-24) years; 10 (66.7%) patients had new-onset AOSD. RA patients had swelling or tender joints. The SLE Disease Activity Index in SLE patients was >8. SS and SSc patients were not on corticosteroids or immunosuppressants. Disease activity in AOSD patients was assessed using Pouchot's score (5). Active AOSD patients were defined as those with AOSD-related symptoms who required additional AOSD treatment; they all had Pouchot's scores of >2 (median, 5[2–10]). Follow-up samples were collected from all AOSD patients with no symptoms, AOSD-related laboratory abnormalities, or Pouchot's score 0 (inactive AOSD).

Serum aldolase levels were significantly higher in active AOSD patients [median, 14.8 (4.3–85.7) U/L; Wilcoxon's signed-rank test] than in inactive AOSD patients [5.8 (3.6–11.6) U/L, $p<0.01$] and control groups [RA, 3.29 (1.7–7.0) U/L, $p<0.01$; SS, 3.3(1.0–4.9) U/L, $p<0.01$; SLE, 4.67(2.3–18.9) U/L, $p<0.01$; and SSc, 3.3 (1.8–6.2) U/L, $p<0.01$; Mann-Whitney U-test] (Fig. 1). One study revealed that AOSD patients with systemic scores > 7 were at high risk of developing complications (7). We found that the serum aldolase levels were higher in patients with systemic scores > 7 (29.95 [12.1-52.8] vs. 12.40 [4.3-85.7] U/L; $p=0.28$ (Mann-Whitney U-test).

ROC-AUC for detecting AOSD determined 8.40 U/L as the reference aldolase level; the respective sensitivity and specificity in comparison with the controls were 80%-93.3% and 100%, respectively. Among active and inactive AOSD patients, aldolase positively correlated with Pouchot's score (r=0.81, $p<0.01$), ferritin (r=0.71, $p<0.01$), C-reactive protein (CRP) (r=0.52, $p<0.01$), aspartate transaminase (AST) (r=0.64, $p<0.01$), and alanine transaminase (ALT) (r=0.45, $p<0.01$) levels but not with creatine kinase (CK) levels [Spearman's rank correlation analysis].

Another study reported increased serum aldolase levels and normal-to-low CK levels in AOSD patients (6). We found that serum aldolase levels were increased in 13 of 14 patients with active AOSD, in the absence of increased CK levels. In patients with eosinophilic fasciitis, serum aldolase levels reportedly increased without an increase in CK levels (8). These data suggest that the serum aldolase in AOSD patients does not originate from muscle tissue, but rather from the fascia. $^{18}$F-fluorodeoxoxyglucose (FDG) positron emission tomography/computed tomography showed that FDG accumulated in the bone marrow (100%) and spleen (96.15%) of AOSD patients (9). Serum aldolase levels were reported to be high in leukemia patients (10). Therefore, the increased serum aldolase levels in AOSD patients may be attributable to haematopoietic hypermetabolism.

Our sample was small; further studies with larger sample sizes are required to evaluate the sensitivity and specificity of the serum aldolase level for AOSD compared to other diseases. In conclusion, serum aldolase may be a useful biomarker for the diagnosis and evaluation of disease activity in AOSD patients.

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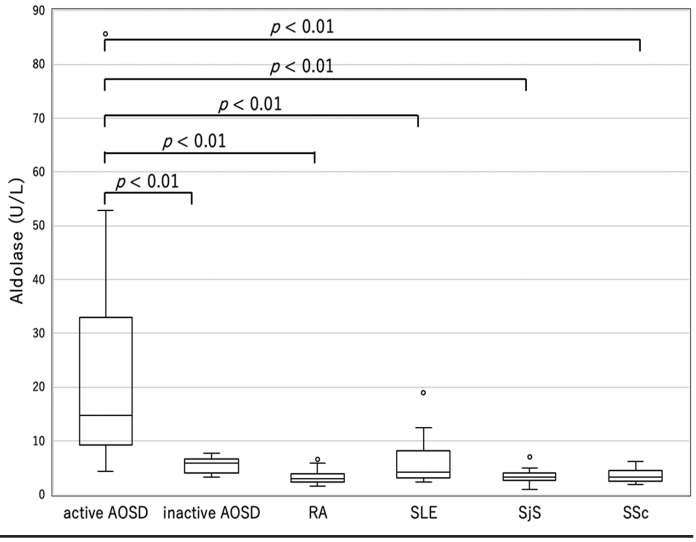


**Fig. 1.** Box plot of the serum aldolase levels in patients with active adult-onset Still's disease (AOSD) (n=15), inactive AOSD, rheumatoid arthritis (RA) (n=30), systemic lupus erythematosus (SLE) (n=30), Sjögren's syndrome (SS) (n=35) and systemic sclerosis (SSc) (n=15).

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