Clinical features of liver dysfunction in collagen diseases

Original article

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Running title: Liver dysfunction in collagen disease.

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ABSTRACT

Aim: Liver dysfunction is not rare in patients with collagen disease. We sought to elucidate the clinical features of liver dysfunction in the presence of collagen disease.

Methods: We analyzed the frequency and causes of liver dysfunction in 607 patients (rheumatoid arthritis (RA), n=220; systemic lupus erythematosus (SLE), n=164; systemic sclerosis (SSc), n=47; Sjögren's syndrome (SjS), n=44; Behçet disease, n=43; polymyositis/dermatomyositis (PM/DM), n=27; vasculitis syndrome, n=25; mixed connective tissue disease (MCTD), n=21; and adult-onset Still's disease (AOSD), n=16).

Results: Liver dysfunction was observed in 238 (39.2%) of 607 patients showing collagen disease. Patients with AOSD (81.3%), PM/DM (51.9%) and vasculitis syndrome (48.0%) frequently displayed liver dysfunction. Liver dysfunction in collagen diseases results from many causes; drug-induced liver injury (26.1%), fatty liver (7.6%), viral hepatitis (1.3%), AIH (4.2%), PBC (15.9%) and the collagen disease itself (15.5%). Conversely, primary biliary cirrhosis was a leading cause in SSc (76.1%) and SjS (70.0%). Liver dysfunction in collagen disease tended to be mild. In addition, alanine aminotransferase levels correlated positively with ferritin levels in AOSD ($R=0.708$, $P<0.05$). Moreover, alkaline phosphatase levels correlated positively with C reactive protein levels in vasculitis syndrome($R=0.833$, $P<0.05$).

Conclusions: Liver dysfunction in the presence of collagen disease has various causes, and

dysfunction associated with collagen disease reflects the activity of the collagen disease itself.

Key words: collagen disease; liver dysfunction

INTRODUCTION

Collagen diseases affect multiple organs, including the liver. Liver dysfunction can arise not only due to the collagen disease itself, but also from various other causes, such as drug toxicity, fatty infiltration, or overlapping autoimmune liver disease[1]. Collagen diseases are systemic, but tend to affect specific organs. Liver dysfunction is not rare in patients with collagen diseases[1,2] and is associated with specific problems in this situation. For example, liver dysfunction in the presence of systemic lupus erythematosus (SLE) is difficult to distinguish from autoimmune hepatitis (AIH), with both SLE and AIH showing similar laboratory findings. In addition, patients with collagen diseases are often treated using corticosteroids, immunosuppressive drugs and biological agents such as anti-tumor necrosis factor and anti-interleukin (IL)-6. As a result, these patients are at risk of de novo hepatitis B. Despite these problems, few reports have described liver dysfunction against a background of collagen disease. Liver dysfunction in the presence of collagen disease is typically mild and temporary, so the causes are often overlooked. This study examined the clinical features of liver dysfunction in patients with collagen diseases and discussed the problems in identifying causes and in managing such dysfunction.

METHODS

Patients

We analyzed 607 patients who had been clinically diagnosed with collagen diseases. Underlying pathologies comprised rheumatoid arthritis (RA) in 220 patients, SLE in 164 patients, systemic sclerosis (SSc) in 47 patients, Sjögren's syndrome (SjS) in 44 patients, Behçet disease (BD) in 43 patients, polymyositis/dermatomyositis (PM/DM) in 27 patients, vasculitis syndrome in 25 patients, mixed connective tissue disease (MCTD) in 21 patients, and adult-onset Still's disease (AOSD) in 16 patients. Diagnoses of collagen diseases were made on the basis of the criteria described by the American College of Rheumatology for RA[3], SLE[4], and SSc[5], the European community for SjS[6], Bohan and Peter[7] for PM/DM, and Kasukawa et al.[8] for MCTD.

Study protocols

Patients were examined for evidence of liver dysfunction, defined by elevations in serum levels of alanine aminotransferase (ALT) (normal, <42 IU/l) or alkaline phosphatase (ALP) (normal, <359 IU/l). Moreover, gamma-glutamyl transpeptide (γGTP) (normal, <48 IU/l) was evaluated. Patients were classified as showing liver dysfunction when the results of at least two different tests were outside the normal range. Patients were categorized according to clinical diagnosis. The diagnosis of drug-induced liver injury was based on the Japanese diagnostic scoring system[9]. We diagnosed as drug-induced liver injury when the score was above 5, indicating a high possibility that the case was a drug-induced liver injury. Structural abnormality and diagnosis of fatty liver were evaluated by

ultrasonography and computed tomography. As virus markers, hepatitis B surface antigen and hepatitis C antibody were screened for. Diagnoses of AIH and primary biliary cirrhosis (PBC) were based on the criteria provided by Jonson and McFarlane[10] and Sasaki et al.[11], respectively. Liver dysfunction without any cause other than the collagen disease itself or that improved in parallel with recovery of collagen diseases was classified as liver disease associated with collagen diseases. Moreover, the degree of liver dysfunction was compared with the activity of each category. Liver histology was evaluated for diagnosis in some patients (RA in 4 patients, SLE in 10 patients, SSc in 16 patients, SjS in 16 patients, PM/DM in 3 patients). Patients for whom causes of liver dysfunction were not examined were classified as "unknown". Continuous variables are expressed as mean ±standard deviation. Non-parametric values are denoted by median values. Values of $p<0.05$ were considered statistically significant.

RESULTS

Incidence of liver dysfunction in collagen diseases (Table 1)

Liver dysfunction was observed in 238 (39.2%) of 607 patientswith collagen disease. Frequency of liver dysfunction was highest in AOSD (81.3%), high in PM/DM (51.9%) and vasculitis syndrome (48.0%), and low in BD (27.9%).

Causes of liver dysfunction (Table 2)

Liver dysfunction in patients with collagen disease can result from many causes: drug-induced liver injury (26.1%); fatty liver (7.6%); viral hepatitis (1.3%); AIH (4.2%); PBC (15.9%); and the collagen disease itself (15.5%). The causes of liver dysfunction differ with each disease. The collagen disease itself was the main cause in patients with AOSD (100%), PM/DM (64.3%), and vasculitis syndrome (58.3%). Drug-induced liver injury was a common cause of liver dysfunction and was particularly prevalent in MCTD (42.9%), RA (40.5%), BD (33.3%) and SLE (31.7%), respectively. The major causative agent for drug-induced liver dysfunction was methotrexate in RA and antibiotics in SLE. PBC was a leading cause of liver dysfunction in SSc (76.1%) and SjS (70.0%). Moreover, the cause was often unknown in patients other than those with AOSD. Few patients showed liver dysfunction due to hepatitis B or C.

Degree of liver dysfunction in collagen disease (Figure 1)

Degree of liver dysfunction in patients with collagen disease was, on the whole, mild. ALT levels (a) are higher in patients with AOSD than those with other collagen diseases .Conversely, ALP levels (b) are higher in patients with SSc, vasculitis syndrome and SjS than those with other collagen diseases. Moreover, γGTP levels (c) are higher in patients with vasculitis syndrome than those with other collagen diseases.

Relationship between degree of liver dysfunction and activity of each collagen disease

In patients with AOSD, ALT levels correlated positively with ferritin ($r=0.708$; $p<0.05$). In patients with vasculitis syndrome, ALP levels correlated positively with levels of C-reactive protein (CRP) ($r=0.833$; $p<0.05$). In patients with other collagen diseases, neither ALT nor ALP levels showed correlations with markers of disease activity.

DISCUSSION

In the present study, liver dysfunction was seen in 39.2% of collagen disease patients. The frequency of liver dysfunction appears to depend on the original collagen disease, with dysfunction seen more frequently in patients with AOSD, PM/DM, and vasculitis syndrome. Previous papers have reported similar tendencies. Rates of liver dysfunction in AOSD, PM/DM and vasculitis syndrome have been reported as about 35-85%, 30% and 54%, respectively[1,12-14]. Interestingly, the main cause of liver dysfunction in these diseases is associated with the original collagen disease. The degree of liver dysfunction thus reflects the activity of the original disease and liver enzymes improve in parallel with recovery of the collagen disease following corticosteroids treatment. In fact, ALT or ALP levels correlated with the disease activity in patients with AOSD and vasculitis syndrome. In contrast to them, in patients with PM/DM, ALT levels didn't correlate

with creatine phosphokinase (CK). CK levels generally reflect the activity of myositis[15], however, dermatomyositis without CK elevation are rarely observed[16]. In this study, one DM patient with liver dysfunction showed normal CK levels. Consequently, ALT levels didn't correlate with CK levels in patients with PM/DM. Although autoimmune mechanism is concerned with the liver dysfunction in collagen diseases, detailed pathogenesis is unknown. It is reported that their main histological findings of the liver are arteritis, and some patient shows chronic active hepatitis or nonspecific reactive hepatitis[17]. In this study, one SLE patient with liver dysfunction showed nonspecific reactive hepatitis.

The causes of liver dysfunction showed some tendency toward associations with the original collagen disease. In the present study, drug-related effects were the most frequent causes of liver dysfunction in patients with RA and SLE. Conversely, the leading cause of liver dysfunction in SLE has been reported as SLE itself, with the degree of liver dysfunction correlating with disease activity[1]. These differences may depend on elapsed time from onset of the disease. In this study, liver dysfunction appeared long after onset of SLE, so activity of SLE was relatively mild. Moreover, many cases were not examined for causes of liver dysfunction because the dysfunction was mild or temporary, although histological examination of the liver is useful in making a differential diagnosis between AIH and SLE-associated hepatitis[18]. The frequency of SLE-associated liver dysfunction might thus be lower than previously reported.

In the present study, no patients showed liver dysfunction due to hepatitis B. However, de novo hepatitis B has recently become a serious problem in patients undergoing chemotherapy or steroid therapy[19]. Fulminant hepatic failure due to de novo hepatitis B is lethal[20]. The possibility of hepatitis B should thus be investigated in patients receiving steroid therapy to prevent fulminant hepatic failure. In particular, checking the HB core and HB surface antibodies is important in HBs antigen negative patients. Moreover, anti-viral drugs should be started according to the guidelines if the existence of HBV is confirmed[21].

Liver dysfunction is generally classifiable into liver cell damage and biliary tract damage. The pattern of liver dysfunction depends on the cause and underlying collagen disease. In this study, ALP levels were elevated in patients with SSc and SjS, in whom liver dysfunction was caused by PBC. Moreover, ALT and ALP levels were elevated in patients with AOSD and vasculitis syndrome, respectively. Liver dysfunction is a major feature in patients with AOSD, and is thus included among the criteria for AOSD[12]. We supposed that the pattern of liver dysfunction in AOSD was liver cell damage on the basis of elevated ALT levels and histological findings, although the precise mechanisms remain unclear. In this study, ALT levels correlated positively with ferritin, reflecting the activity of AOSD[22]. Previous studies have reported elevated ALP levels as characteristic in patients with vasculitis, reflecting the involvement of small intrahepatic vessels causing ischemic cholangitis[23,24]. In the present study, ALP levels correlated positively with CRP, reflecting the

activity of vasculitis syndrome [25]

Autoimmune liver diseases such as AIH and PBC sometimes complicate collagen disease. In particular, the present study revealed PBC as a leading cause of liver dysfunction in SSc and SjS. PBC should be considered when liver dysfunction is identified in patients with SSc or SjS.

No patients in this study exhibited severe liver failure. Liver dysfunction in patients with collagen disease is generally mild and the prognosis is good irrespective of the cause[1,26,27]. The use of steroid administration is one probably reason for such positive outcomes. On the other hand, some investigations have reported severe hepatic failure in AOSD[28-30]. Such liver failure developed during steroid therapy long after onset of AOSD. Moreover, Ott et al. reported a patient with AOSD in whom hepatic failure developed when other symptoms were well controlled by corticosteroid treatment[30]. Clinicians thus need to remain vigilant for liver dysfunction in AOSD.

In conclusion, liver dysfunction in patients with collagen diseases shows specific tendencies for each collagen disease. Understanding the features of liver dysfunction is necessary when treating collagen disease.

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Figure legends.

Degree of liver dysfunction in collagen disease. ALT, ALP, and γGTP levels were evaluated. ALT levels (a) are higher in patients with AOSD than those with other collagen diseases . ALP levels (b) are higher in patients with SSc, vasculitis syndrome and SjS than those with other collagen diseases. γGTP levels (c) are higher in patients with vasculitis syndrome than those with other collagen diseases. The data represent mean±SD. *Statistically significant differences between the indicated diseases ($P<0.05$). RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; SjS, Sjögren's syndrome; BD, Behçet disease; PM, polymyositis; DM, dermatomyositis; MCTD, mixed connective tissue disease; AOSD, adult onset Still's disease

Table1. Clinical findings in 607 patients with collagen disease

	No. of patients	Sex (male/female)	Age (yrs)	Prevalence of liver dysfunction
RA	220	38/182	59.1±13.8	79 (35.9%)
SLE	164	31/133	42.3±16.8	60 (36.6%)
SSc	47	8/39	58.7±13.7	21 (44.7%)
SjS	44	5/39	57.9±14.2	20 (45.5%)
BD	43	15/28	52.6±15.3	12 (27.9%)
PM/DM	27	3/24	57.6±13.5	14 (51.9%)
Vasculitis	25	4/21	52.2±18.8	12 (48.0%)
MCTD	21	2/19	58.2±11.4	7 (33.3%)
AOSD	16	2/14	38.0±4.8	13 (81.3%)
Total	607	108/499	52.9±7.8	238 (39.2%)

RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; SjS, Sjögren's syndrome;
BD, Behçet disease; PM, polymyositis; DM, dermatomyositis; MCTD, mixed connective tissue disease;
AOSD, adult onset Still's disease

Table 2 The cause of liver dysfunction

	No. of patients	collagen disease	drug	fatty liver	HBV	HCV	PBC	AIH	unknown
RA	79	2(2.5%)	32(40.5%)	5(6.3%)	0	1(1.3%)	3(3.8%)	1(1.3%)	35(44.3%)
SLE	60	3(5.0%)	19(31.7%)	10(16.7%)	0	2(3.3%)	3(5.0%)	6(10.0%)	17(28.3%)
SSc	21	1(4.8%)	1(4.8%)	0	0	0	16(76.1%)	0	3(14.3%)
SjS	20	0	1(5.0%)	0	0	0	14(70.0%)	2(10.0%)	3(15.0%)
BD	12	2(16.7%)	4(33.3%)	2(16.7%)	0	0	0	0	4(33.3%)
PM/DM	14	9(64.3%)	1(7.1%)	0	0	0	2(14.3%)	1(7.1%)	1(7.1%)
Vasculitis	12	7(58.3%)	1(8.3%)	0	0	0	0	0	4(33.3%)
MCTD	7	0	3(42.9%)	1(14.2%)	0	0	0	0	3(42.9%)
AOSD	13	13(100%)	0	0	0	0	0	0	0
Total	238	37(15.5%)	62(26.1%)	18(7.6%)	0	3 (1.3%)	38 (15.9%)	10(4.2%)	70(29.4%)

RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; SjS, Sjogren s syndrome; BD, Behçet disease; PM, polymyositis; DM, dermatomyositis; MCTD, mixed connective tissue disease; AOSD, adult onset Still's disease

Figure 1 a

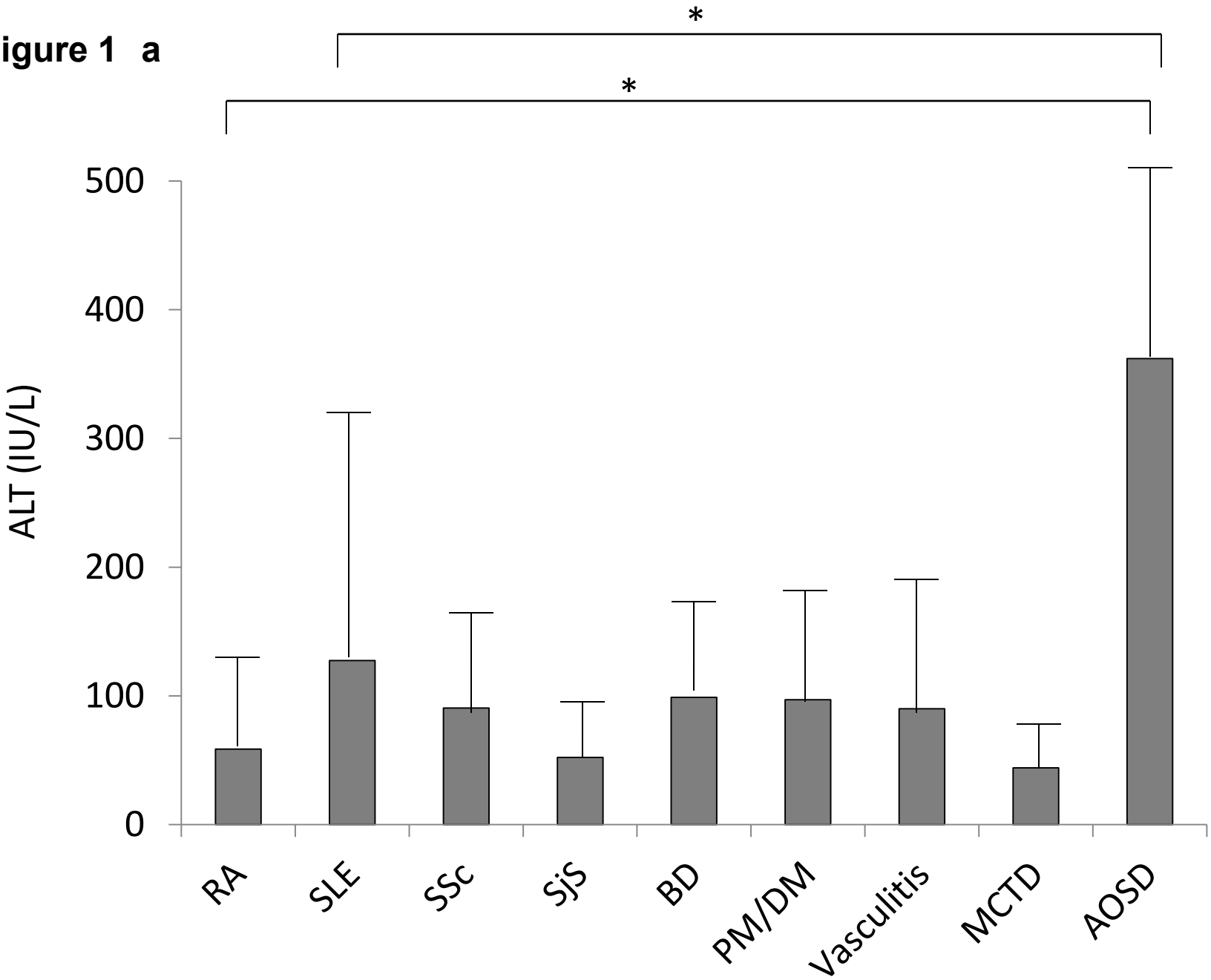
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Figure 1 b

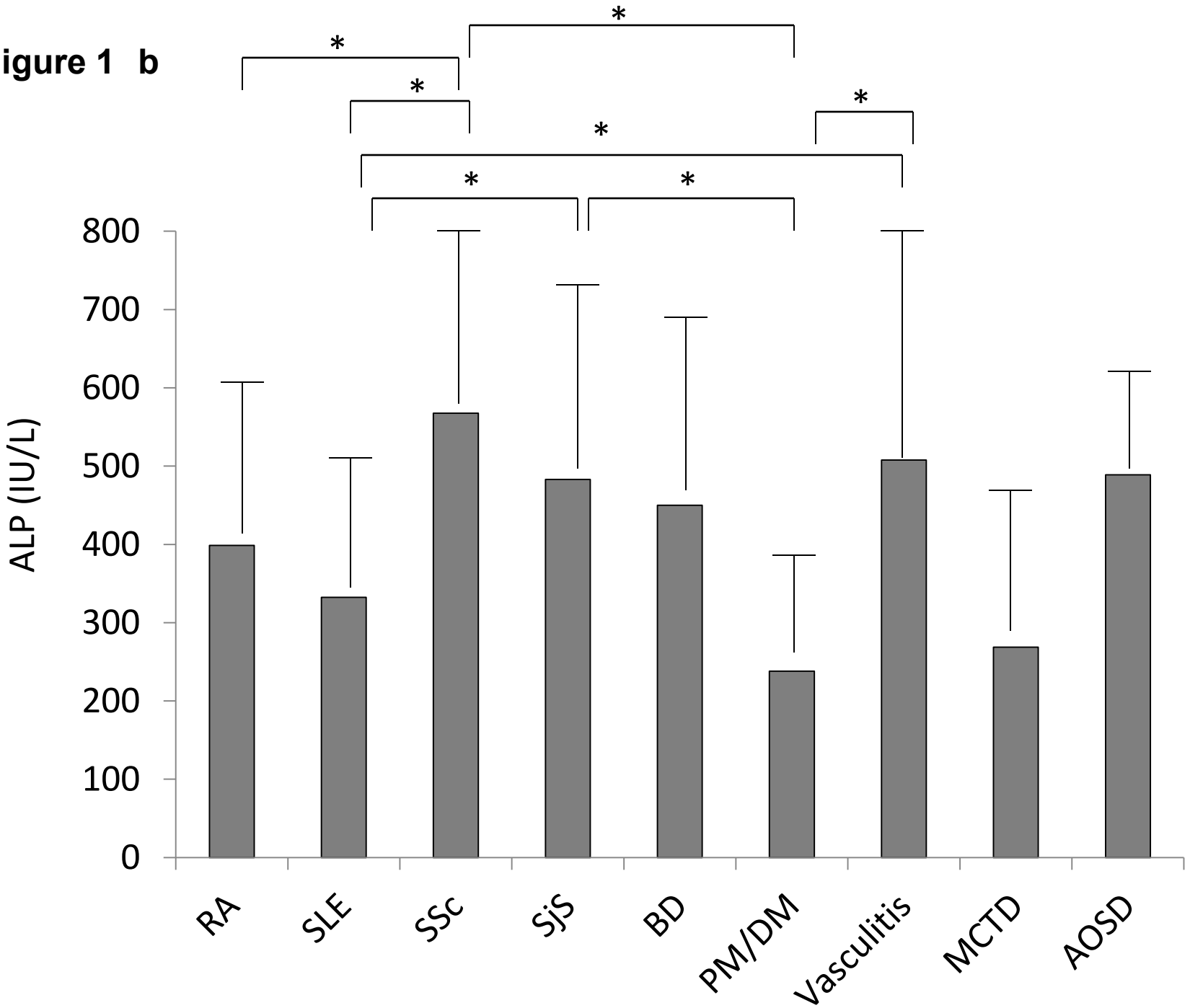
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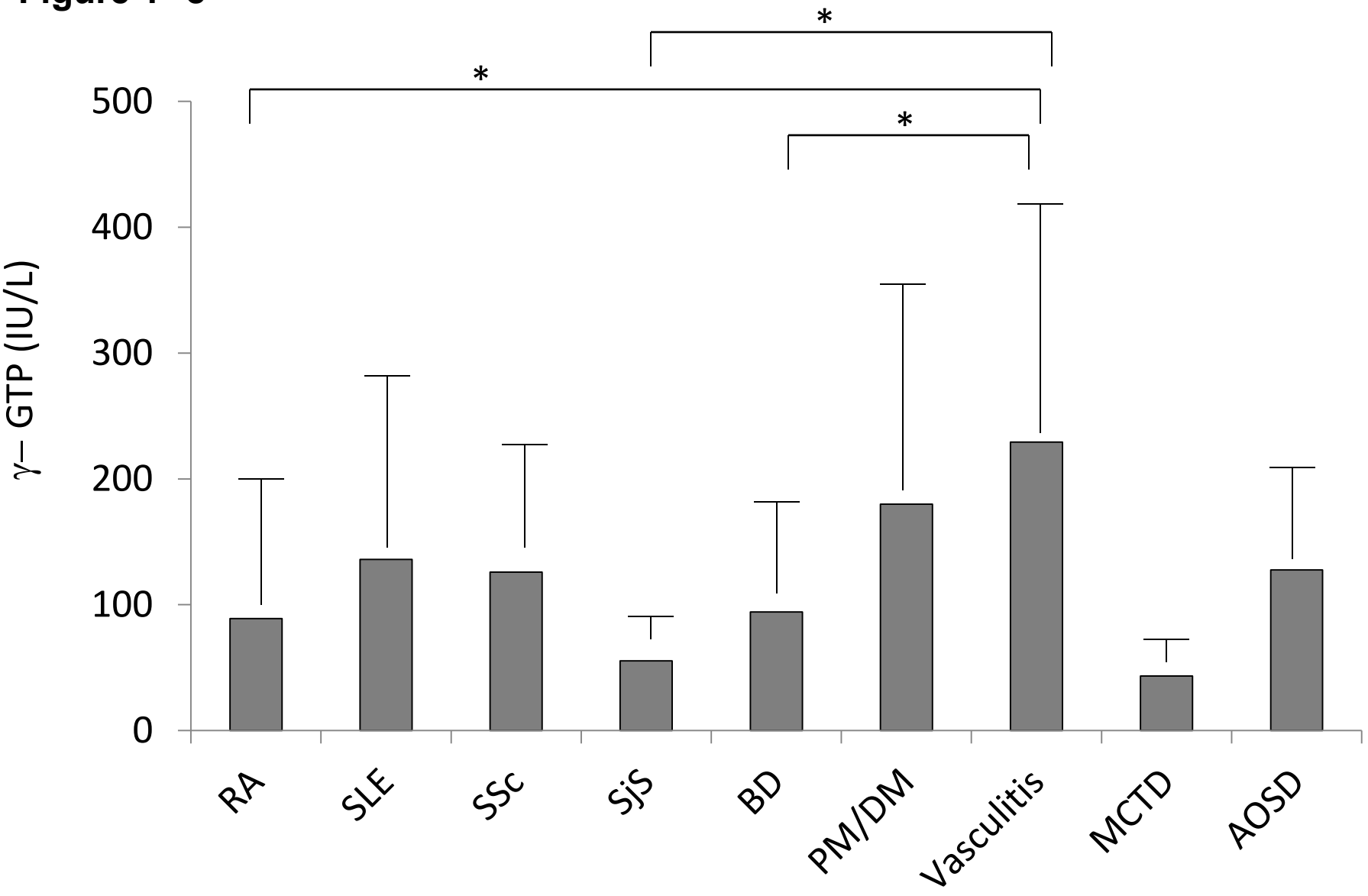
Figure 1 c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