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Clinical significance of anti-DNA/N-methyl-D-aspartate receptor 2 antibodies in *de novo* and post-steroid neuropsychiatric systemic lupus erythematosus

Running title

Anti-DNA/NR2 antibodies in *de novo* and post-steroid NPSLE

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Conflict of Interest Statement

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Pharmaceutical K.K. ASAHI KASEI PHARMA CORPORATION, Eisai Co.,
Alexion Inc., and Mitsubishi Tanabe Pharma Co.

The other authors declare that they have no conflict of interest.

Abstract

Background: Anti-DNA/ N-methyl-D-aspartate receptor 2 (NR2) antibodies (anti-DNA/NR2 antibodies) are a subset of anti DNA autoantibodies that cross-react with the extracellular domain of the GluN2A/GluN2B subunits of NR2. These antibodies induce apoptosis of hippocampus neurons and psychiatric disorder in mice and humans. Neuropsychiatric SLE (NPSLE) can develop after initiation of corticosteroids (post-steroid neuropsychiatric manifestation: PSNP) or before treatment (*de novo* NPSLE), however, pathophysiological differences between these subtypes remain unclear. The objective of this study was to clarify the prevalence of anti-DNA/NR2 antibodies in patients with NPSLE. **Methods:** This study involved a cohort of

patients with NPSLE admitted to our hospital. NPSLE patients were classified into two groups, *de novo* NPSLE and PSNP-SLE. Serum anti-DNA antibodies and anti-DNA/NR2 antibodies were measured by ELISAs.

Results: Serum samples were obtained from 24 patients with *de novo* NPSLE, 25 with PSNP-SLE and 76 healthy controls (HC). The level of anti-DNA/NR2 antibodies in patients with *de novo* NPSLE and PSNP-SLE were also higher than those in HC. Positive correlation between anti-DNA antibodies and anti-DNA/NR2 antibodies were found in PSNP-SLE, but not significant in *de novo* NPSLE.

Conclusion: The levels of anti-DNA/NR2 antibodies in PSNP-SLE were similar to those in *de novo* NPSLE. Anti-DNA/NR2 antibodies in PSNP-SLE were suggested as dominant subset of anti-DNA antibodies, indicating that anti-DNA/NR2 antibodies may be a predictive factor in PSNP-SLE.

Key words

Systemic lupus erythematosus (SLE), post steroid neuropsychiatric manifestation (PSNP), neuropsychiatric systemic lupus erythematosus (NPSLE), N-Methyl D-aspartate receptors (NMDAR), anti-NR2 antibody

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by production of various autoantibodies and development of various organ damages(1). In particular, neuropsychiatric SLE (NPSLE) involves a number of different neurologic and psychiatric syndromes, being recognized as the most difficult clinical condition to diagnose as well as to treat, thus remaining as a major cause of morbidity and mortality in this disease(2).

Anti-DNA/NR2 antibodies are a subset of anti-DNA autoantibodies that cross-react with N-Methyl D-aspartate receptors (NMDARs) and are considered as one of the pathogenic antibodies cause of NPSLE(3, 4). NMDA is a glutamate receptor and ion channel protein found in nerve cells that is a major excitatory neurotransmitter in brain involved in synaptic plasticity and memory function. The receptors consist of NMDAR subunit 1 (GluN1) and subunit 2 [GluN2 (A,B,C or D)](5). The anti-DNA/NR2 antibodies binds to GluN2A and GluN2B subunits (NR2) of the NMDAR containing the

consensus peptide sequence D/EWD/EYS/G (DWEYS) located in the extracellular domain (6). Anti-DNA/NR2 antibodies exhibit dose-dependent neurotoxicity in both humans and mouse models (7). The presence of anti-DNA/NR2 antibodies, particularly in cerebrospinal fluid from NPSLE patients was associated with developing psychiatric manifestations (4). The levels of anti-DNA/NMDAR antibodies are elevated also in sera from patients from active NPSLE(8, 9).

In patients with SLE, neuropsychiatric (NP) symptoms sometimes occur after administration of corticosteroids, making it challenging for clinicians to differentiate NPSLE and steroid-induced psychosis. We recently reported that post-steroid NP manifestations (PSNP) are strikingly more frequent in patients with SLE defined as PSNP-SLE, compared with other systemic autoimmune diseases(10). Of PSNP-SLE patients, two – thirds were with one or more abnormal findings in cerebrospinal fluid, electroencephalogram, MRI or SPECT. It is more than difficult to judge PSNP are due to lupus or to corticosteroids. However, majorities of the patients with PSNP in SLE

improved with intensified immunosuppressive treatments without rapid tapering or withdrawal of corticosteroids, indicating that PSNP is one of the clinical features of NPSLE. Hence, we defined the SLE patients who develop post-steroid NP manifestation as PSNP-SLE and who develop NPSLE before initiation of high-dose corticosteroids as *de novo* NPSLE. SLE patients who develop post-steroid NP manifestation (PSNP-SLE) have better prognosis compared with SLE patients who had neuropsychiatric manifestations on their admission (*de novo* NPSLE). However, these findings have not yet fully been supported from the immunological point of view.

Here, we investigate the clinical significance of anti-DNA/NR2 antibody in PSNP-SLE and *de novo* NPSLE.

Methods

Patients and controls

This retrospective study comprised 24 patients with *de novo* NPSLE, 25 with PSNP-SLE whom we had frozen serum aliquots stored from our previous

study group (10) in Hokkaido University Hospital during the period between April 2002 and March 2015. All patients were admitted due to SLE with high disease activity. Healthy control (HC) sera were obtained from the Bioreclamation IVT bank (United States) (n=76). This study has been approved by the local ethical committee of Hokkaido University Hospital (approve number: 015-0281). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Data collection

All SLE patients fulfilled the 1997 revised SLE classification criteria of the American College of Rheumatology(11). NP events in SLE patients were classified according to the American College of Rheumatology nomenclature

of NPSLE in 1999(12). Headache was excluded from evaluation in this study because of its low specificity for NPSLE (13). Two experienced psychiatrists evaluated the symptoms of the patients according to the ACR classification of NP manifestation. NPSLE was divided into the 2 subgroups namely diffuse manifestation or focal manifestation including central nervous system or peripheral nervous system according to the ACR classification. The following data were evaluated at the time of admission: sex, age on admission and at onset, disease duration, past history of mental disorder, past treatment, initial therapy after admission, serum C3, anti-U1-RNP, anti-Sm, and anti-SS-A/Ro antibodies. Complication by antiphospholipid syndrome (APS) was assessed according to the Sydney-revised Sapporo criteria(14). Disease activity was evaluated using Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K)(15). Lupus nephritis was diagnosed by renal biopsy.

Definition of PSNP-SLE and de novo NPSLE

de novo NPSLE is defined as primary NPSLE diagnosed before initiation of

high-dose corticosteroids. PSNP-SLE is defined as neuropsychiatric manifestations occurred after initiation of corticosteroids(10).

Laboratory analysis

All serum samples were analyzed for the presence of anti-DNA and anti-DNA/NR2 antibodies by in-house enzyme-linked immunosorbent assay (ELISA) as previously described (16). In brief, anti-DNA/NR2 antibodies were detected by specific ELISA using the 283-287-pentapeptide consensus sequence of human NMDA receptor GluN2A and GluN2B subunits. All the analyzed sera were collected from patients showing their active disease states and were stored at -80°C until use.

The anti-DNA/NR2 antibody titer (arbitrary units: AUs) of each sample was derived from a standard curve according to serial dilutions of the positive control (17, 18). Normal ranges of anti-DNA/NR2 antibody with cut-off values of 99th percentile were established using 76 healthy controls.

Statistical analysis

Statistical evaluation was carried out by Fisher's exact test, Mann-Whitney

U-test, Spearman's correlation, analysis of covariance (ANCOVA) and Kruskal-Wallis test with the Dunn multiple comparison test, as appropriate. P values less than 0.05 were considered significant. Calculations were made, using JMP®12.2.0 (SAS Institute Inc, Cary, North Carolina, USA).

Results

Characteristics of patients

Serum samples were obtained from 24 patients with *de novo* NPSLE, 25 with PSNP-SLE and 76 healthy controls. Clinical features of the patients are illustrated in Table 1. In PSNP-SLE patients, clinical features were evaluated before developing neuropsychiatric manifestations. The clinical characteristics included frequency of female patients, complication with APS, lupus nephritis, median age at onset and disease duration, which were similar between *de novo* NPSLE and PSNP-SLE. However, SLEDAI-2K in *de novo* NPSLE was higher than PSNP-SLE (Table 1). There were no differences in serum C3, anti-U1-RNP, anti-Sm, anti-SS-A/Ro antibodies

(data not shown). There were significant differences in NPSLE subtypes between the two groups (Table 2). The focal manifestation, especially cerebrovascular disease was more frequent in *de novo* NPSLE than in PSNP-SLE, even though the prevalence of antiphospholipid antibodies was similar between the two groups. On the other hand, diffuse manifestation, especially acute confusional state (ACS) and mood disorder was more frequent in PSNP-SLE than in *de novo* NPSLE.

Measurement of serum anti-DNA antibody and anti-DNA/NR2 antibody in de novo NPSLE, PSNP-SLE and HC

The median AUs (IQR: Interquartile Range) of anti-DNA antibodies in *de novo* NPSLE, PSNP-SLE and HC were 150.3 (100.8-190.7), 172 (108.9-224.4) and 14.3 (11.8-17.8). The median AUs (IQR) of anti-DNA/NR2 antibodies in *de novo* NPSLE, PSNP-SLE and HC were 25.1 (12.9-76.1), 13.4 (11.1-19.6) and 14.3 (11.8-17.8), respectively.

Anti- DNA antibody levels were significantly elevated in *de novo* NPSLE and

PSNP-SLE compared with healthy controls (Figure 1A). Similarly, anti-DNA/NR2 antibody levels were significantly elevated in *de novo* NPSLE and PSNP-SLE compared with healthy controls (Figure 1B). There was no significant difference in the levels of these autoantibodies between *de novo* NPSLE and PSNP-SLE. Anti-DNA antibody levels were confirmed by commercial ELISA kit (MESACUP™DNA-II TEST: Medical & Biological Laboratories Co. Ltd., Nagoya, Japan), showing similar tendency (Supplementary).

Correlation coefficients between the AUs of serum anti-DNA antibody and anti-DNA/NR2 antibody in de novo NPSLE, PSNP-SLE

Because anti-DNA/NR2 antibody is one of the subsets of anti-DNA antibodies, correlation coefficients of the antibodies can indicate how dominant the anti-DNA/NR2 antibodies are in anti-DNA antibodies. The levels of anti-DNA antibodies were positively correlated with the levels of anti-DNA/NR2 antibodies only in patients with PSNP-SLE ($r=0.73$, $p<0.001$)

(Figure 2A and 2B). Such positive correlation was not found in those with *de novo* NPSLE ($r=0.29$, $p=0.17$). The significant difference was observed in regression slopes between *de novo* NPSLE and PSNP-SLE ($p=0.0036$).

Discussion

Here we report for the first time the high titers of anti-DNA/NR2 antibody in patients with PSNP-SLE. Anti-DNA/NR2 levels in PSNP-SLE were similar with *de novo* NPSLE, indicating that PSNP-SLE shares some of the clinical features of NPSLE as we suggested in the previous report (10). Mader et al reported the titers of anti-DNA/NR2 antibodies in NPSLE and SLE without NP manifestations (19), indicating that high titer of anti-DNA/NR2 antibodies may be predictive of NPSLE developing.

The strong correlation between anti-DNA antibodies and anti-DNA/NR2 antibodies found in PSNP-SLE suggests that anti-DNA/NR2 antibodies in PSNP-SLE patients are a dominant population of their anti-DNA antibodies. Because anti-DNA/NR2 antibody binds to NMDA receptors expressed on

neurons and leads to excitotoxic neuronal death in a dose-dependent manner (7), anti-DNA/NR2 carrier is thought to be a high-risk group to develop NPSLE. A previous study also showed that anti-DNA/NR2 antibody was associated with diffuse manifestation (4). Consistent with this, the higher prevalence of diffuse symptoms in PSNP-SLE than in *de novo* NPSLE observed in our study might be associated with the presence of anti-DNA/NR2 antibody. In a previous study, acute confusional state (ACS), a main symptom of diffuse manifestation, was shown to be blood brain barrier (BBB) disruption(20). Interestingly, the prevalence of ACS in PSNP-SLE was higher than in *de novo* NPSLE in our study. Furthermore, 17 of 19 patients with PSNP-SLE whose CSF were examined revealed CSF abnormality (data not shown). Additionally, mood disorder was also frequent in PSNP-SLE. In most of cases, mood disorder was shown as comorbidity with other symptoms such as ACS or psychosis. A breach in the integrity of the BBB was required for antibody to access brain tissue and affect neuronal function and viability(21). According to the animal model, since each drug

can affect different region of BBB, anti-DNA/NR2 antibody can damage different areas of brain leading to variable behavioral changes(21). The characteristic differences between *de novo* NPSLE and PSNP-SLE may be caused by different regional disruptions of the BBB.

Our study comprises some limitations. The current study is a single-centered retrospective observational study with relatively small sample size, where clinical examinations are not done in all of the patients.

The differential diagnosis of NP manifestation between PSNP-SLE and steroid-induced psychosis has been still challenging. In conclusion, anti-DNA/NR2 antibodies may be a predictive factor not only in *de novo* NPSLE, but also in PSNP-SLE. Further analysis will be awaited to improve the diagnostic potential in NPSLE.

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Figure Legends

Figure 1: Measurement of serum anti-DNA antibody and anti-DNA/NR2

antibody in *de novo* NPSLE, PSNP-SLE and HC. (A) Serum anti-DNA

antibody levels in *de novo* NPSLE, PSNP-SLE and HC. (B) Serum anti-DNA

/NR2 antibody levels in *de novo* NPSLE, PSNP-SLE and HC.

de novo NPSLE: *de novo* NPSLE is defined as primary NPSLE diagnosed before initiation of high-dose corticosteroids. PSNP-SLE: PSNP-SLE is neuropsychiatric manifestation occurred after initiation of corticosteroids.

HC: healthy controls. anti-DNA /NR2 antibody: a subset of anti DNA autoantibodies that cross-react with the extracellular domain of the GluN2A/GluN2B subunits of the N-methyl-D-aspartate receptor 2 (NR2).

Statistical analysis was performed by Kruskal-Wallis test with Dunn multiple comparison test.

Figure2: Correlation between anti-DNA antibody and anti-DNA/NR2 antibody in patients with *de novo* NPSLE and PSNP-SLE. (A) Correlation between anti-DNA antibody and anti-DNA/NR2 antibody in *de novo* NPSLE. (B) Correlation between anti-DNA antibody and anti-DNA/NR2 antibody in PSNP-SLE.

de novo NPSLE: *de novo* NPSLE is defined as primary NPSLE diagnosed before initiation of high-dose corticosteroids. PSNP-SLE: PSNP-SLE is

neuropsychiatric manifestation occurred after initiation of corticosteroids.

HC: healthy controls. anti-DNA /NR2 antibody: a subset of anti DNA

autoantibodies that cross-react with the extracellular domain of the

GluN2A/GluN2B subunits of the N-methyl-D-aspartate receptor 2 (NR2).

Statistical analysis was performed by Spearman's rank correlation test.

Table 1

		<i>de novo</i> NPSLE (n=24)		PSNP-SLE (n=25)		<i>p</i>
Female	n (%)	21	(72.4)	21	(80.8)	n.s.
Age at onset (years)	median [IQR]	26	[15 - 42]	22	[16 - 39]	n.s.
Age on admission (years)	median [IQR]	33	[24 - 53]	36	[20 - 47]	n.s.
Disease duration (months)	median [IQR]	29	[2 - 74]	23	[2 - 135]	n.s.
Past history of mental disorder	n (%)	5	(20.8)	6	(24.0)	n.s.
Family history of mental disorder	n (%)	2	(8.3)	2	(8.0)	n.s.
Antiphospholipid antibody carrier	n (%)	3	(12.5)	5	(20.0)	n.s.
Lupus nephritis	n (%)	7	(29.2)	12	(48.0)	n.s.
Past history of treatment						
Daily corticosteroids	n (%)	16	(66.7)	11	(44.0)	n.s.
Steroid pulse	n (%)	3	(12.5)	7	(28.0)	n.s.
Immunosuppressant	n (%)	9	(37.5)	6	(24.0)	n.s.
Disease activity						
SLEDAI-2K	median (IQR)	19	[13 - 23]	12	[7 - 18]	0.0153*

* $P < 0.05$, using Fisher's exact test or Mann-Whitney U-test, comparison between values in *de novo* NPSLE and PSNP-SLE.

IQR, interquartile range: SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000

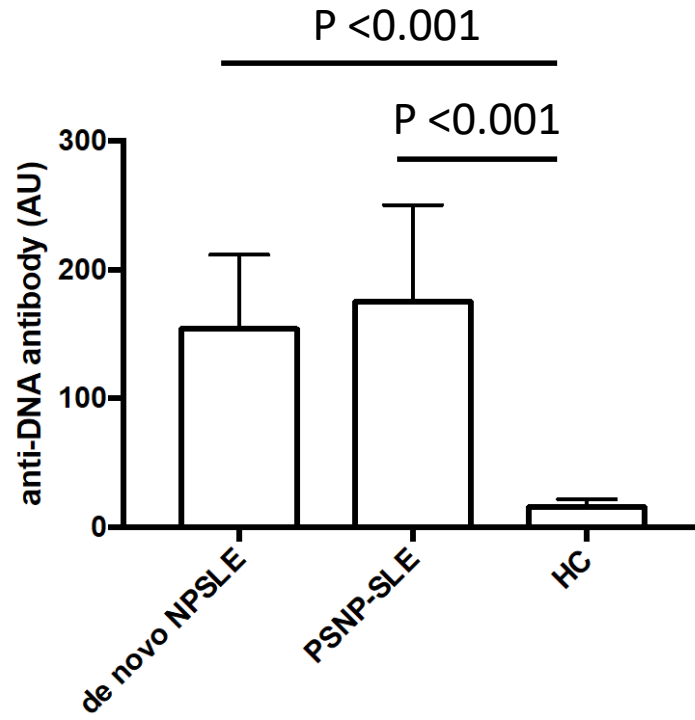
Table 2

		<i>de novo</i> NPSLE (n=24)		PSNP-SLE (n=25)		<i>p</i>
Diffuse manifestation	n (%)	17	(70.8)	24	(96.0)	0.023*
Acute confusional state	n (%)	10	(41.7)	18	(72.0)	0.045*
Mood disorder	n (%)	8	(33.3)	12	(48.0)	0.047*
Psychosis	n (%)	3	(12.5)	7	(28.0)	n.s.
Cognitive dysfunction	n (%)	5	(20.8)	1	(4.0)	n.s.
Anxiety disorder	n (%)	1	(4.2)	3	(12.0)	n.s.
Focal manifestation	n (%)	9	(37.5)	2	(8.0)	0.018*
Central nervous syndrome	n (%)	9	(8.3)	2	(8.0)	n.s.
Peripheral nervous syndrome	n (%)	2	(10.3)	0	(0)	n.s.
Cerebrovascular disease	n (%)	6	(25.0)	1	(4.0)	0.049*
Aseptic meningitis	n (%)	1	(4.2)	0	(2.0)	n.s.
Chorea	n (%)	1	(4.2)	0	(0)	n.s.
Seizures	n (%)	1	(4.2)	1	(4.0)	n.s.
Myelopathy	n (%)	0	(0)	0	(0)	n.s.

* $P < 0.05$, using Fisher's exact test, comparison between values in *de novo* NPSLE and PSNP-SLE.

Figure 1

A



B

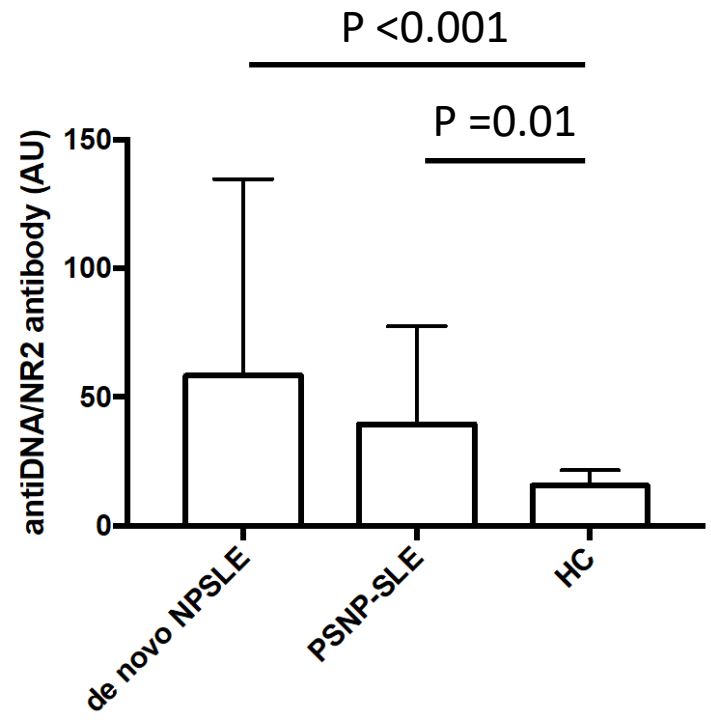
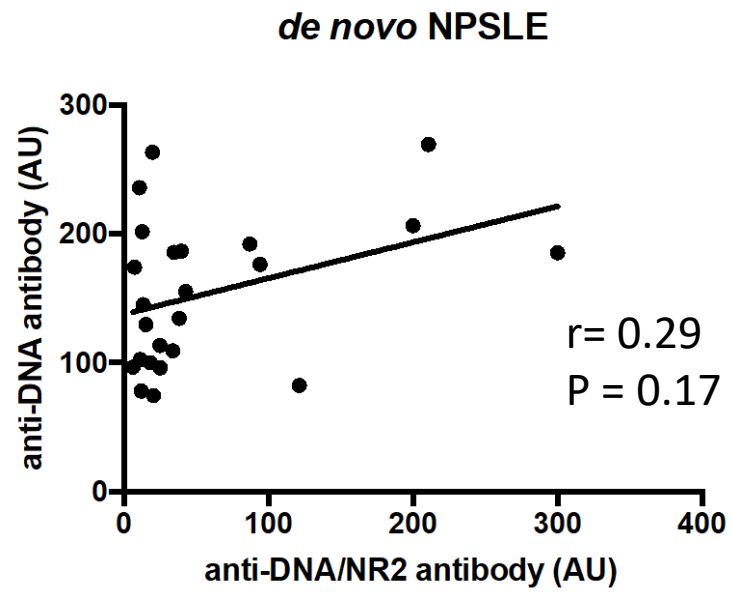
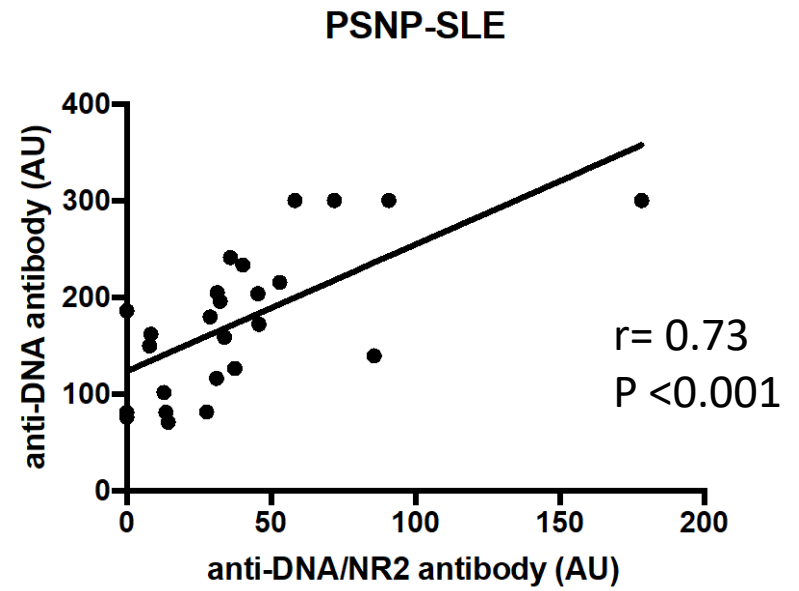


Figure 2

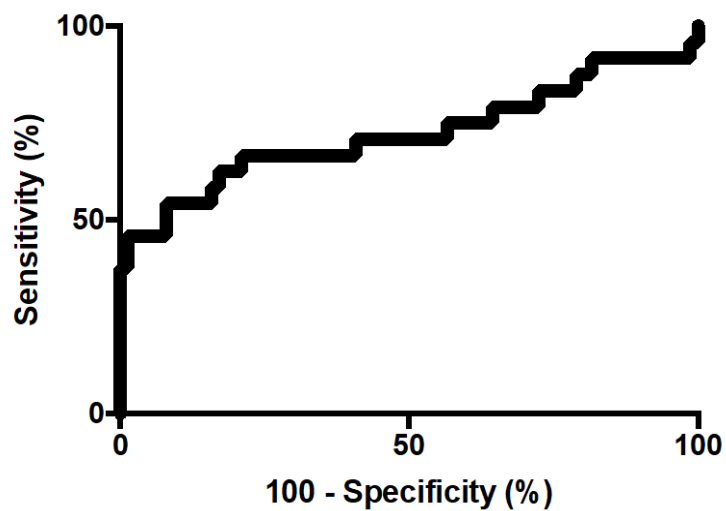
A



B



A



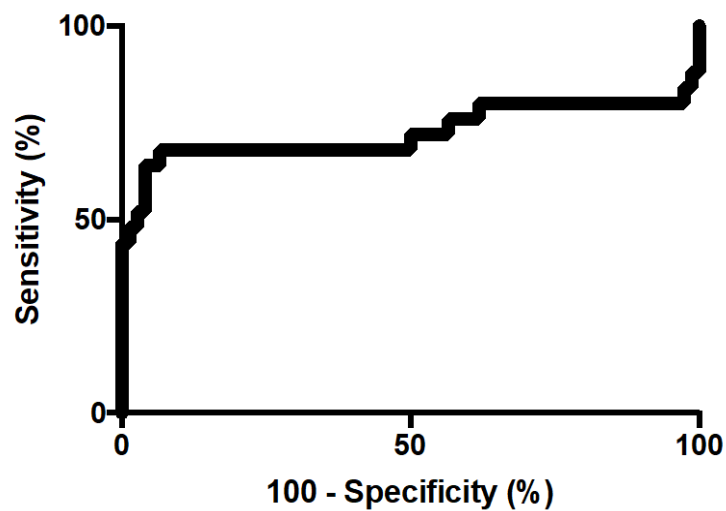
de novo NSPSLE

AUC: 0.723

95% C.I 0.578-0.867

Cutoff: 25.0AU

B



PSNP-SLE

AUC: 0.725

95% C.I 0.567-0.883

Cutoff: 27.7 AU