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NINE-TEST PANEL HAS SUPERIOR SENSITIVITY TO DETECT ANTIPHOSPHOLIPID ANTIBODY SYNDROME IN PATIENTS WITH OR WITHOUT SLE

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Abstract

Anti-phospholipid antibodies (aPL) and lupus anticoagulant (LAC) represent diagnostic criteria for systemic lupus erythematosus (SLE) and underlie anti-phospholipid syndrome (APS) in patients with and without SLE. 526 healthy controls and 1633 SLE and 1835 primary APS (PAPS) patients were evaluated. LAC was assessed by hexagonal phase phospholipid neutralization assay (HPPNA), diluted Russell viper venom test (dRVVT), and platelet neutralization procedure (PNP). β2-glycoprotein-I and cardiolipin IgG, IgM, and IgA antibodies (aCL-IgG, aCL-IgM, aCL-IgA) were measured. 222/1633 SLE patients had APS based on the nine-test panel, which afforded the highest sensitivity (74%) and negative predictive value (90%) but lowest specificity (52%). HPPNA was the most sensitive individual test at 52%. The nine-test panel yielded the greatest sensitivity for aPL detection (70%) relative to HPPNA, the most sensitive individual test (36%) in PAPS. Superior sensitivity of a nine-test aPL panel has major implications for preventing potentially fatal thrombotic events in SLE and PAPS.

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INTRODUCTION

Antiphospholipid syndrome (APS) is characterized by thrombotic events attributed to anti-phospholipid antibodies (aPL) (1). aPL also represent a diagnostic criterion for SLE (2) and elicit significant pathologies in patients with or without lupus (3;4). Most patients have primary APS (PAPS) while a significant minority, over 30%, has SLE or another systemic autoimmune disorder (1;5). In turn, 40% of patient with SLE have antiphospholipid antibodies (aPL), but less than 40% of them will eventually develop APS (6). PAPS affects 0.05% of the population (7;8), however, it may be underdiagnosed in the absence of SLE, which can lead to omission of treatment. Therefore, we assessed the consistency of aPL testing in SLE and non-SLE patients who carried the diagnosis of thromboembolic events, such as deep venous thrombosis (DVT), pulmonary embolism (PE), and or stroke. The results indicate that a nine-test panel, comprising three lupus anticoagulant tests, such as hexagonal phase phospholipid neutralization assay (HPPNA), diluted Russell viper venom test (dRVVT), and platelet neutralization procedure (PNP) as well as measurements of IgG, IgM, and IgA antibodies against β2-glycoprotein 1 (aβ2-IgG, aβ2-IgM, aβ2-IgA) and cardiolipin (aCL-IgG, aCL-IgM, aCL-IgA) has superior sensitivity to detect aPL both in SLE and PAPS. However, the complete panel was only performed in a minority of patients. Among individual tests, HPPNA had the highest sensitivity, and thus, it may be a good initial test for screening for APS. Moreover, given the contribution of aPL as immunologic criterion for diagnosis of SLE (6,7), failure to employ the complete panel with IgA antibodies may lead to exclusion of patients who otherwise meet criteria for a definitive diagnosis. These findings have major implications for the diagnosis of SLE and APS with relevance for prevention of potentially fatal thrombotic events.

PATIENTS AND METHODS

Patients.

The electronic medical records of SUNY Upstate Medical University Hospital were examined for quality improvement with respect to utilization of laboratory tests for detection of APS in patients with and without SLE. Patients were identified by using the slicer-dicer feature of the Epic electronic medical records at Upstate University Hospital between March of 2013 and February of 2018. Clinical diagnoses were based on final diagnosis during hospitalization. 1633 SLE patients, who satisfied the ACR classification criteria for a definitive diagnosis (9;10), were evaluated for the presence of non-obstetric APS events such as DVT, PE, and stoke, as earlier described (3). Among the SLE patients, 1451 were females of 50±18 years of age (range: 3–90 years) and 182 were males of 46±14 years of age (range: 7–94 years). 1,835 non-SLE patients were evaluated for the presence of PAPS. Of those patients, 513 were diagnosed with PE (380 females of 50±15 years of age, range: 17–84 years; 133 males of 53±15 years of age, range: 3–82 years), 583 with DVT (380 females of 51±15 years of age, range: 5–85 years; 133 males of 53±15 years of age, range: 3–82 years), and 739 with stroke (380 females of 52±14 years of age, range: 5–89 years; 133 males of 53±15 years of age, range: 2–87 years). Non-SLE patients screened for thrombotic events compatible with PAPS did not carry the diagnosis of SLE or a positive antinuclear antibody

test. Sera and plasma of 526 healthy blood donors were used as controls for antibody and LAC testing, respectively.

Laboratory methods.

Lupus anticoagulants were assessed by Staclot LA hexagonal phase phospholipid neutralization assay (HPPNA; delta <8 seconds), Staclot diluted Russell viper venom test (dRVVT; <1.2 normalized ratio) obtained from Stago (Parsippany, NJ, USA). Platelet neutralization procedure (PNP; delta < 1 second) has been performed using a Stago STA-R Evolution Instrument, as earlier described (11;12). IgG and IgM antibodies against β2-glycoprotein 1 (aβ2GPI-IgG, aβ2GPI-IgM) and cardiolipin (aCL-IgG, aCL-IgM) were measured in house while IgA isotypes (aβ2GPI-IgA, aCL-IgA) were tested by LabCorp Diagnostics (Burlington, NC). LAC testing was performed by addition of polybrene to plasma from patients treated with heparin (13).

Statistical analysis.

Sensitivities, specificities, positive (PPV) and negative predictive values (NPV) for detection of APS were calculated and compared by 2-tailed chi-square tests using GraphPad software. Differences were considered significant at $p<0.05$ for hypothesis testing.

RESULTS

222 of 1633 SLE patients had APS when using a combination of nine tests. Table 1 shows the frequency of positive and negative test results, sensitivity, specificity, PPV, NPV, and p value for each assay. The greatest sensitivity, 74%, was seen when all nine tests were performed together for detecting APS in SLE patients ($p=0.0003$ versus HPPNA; Table 1). However, combining all tests had the lowest specificity, 52% ($p<0.0001$ versus HPPNA). The complete nine-test panel was only performed in 550 of 1633 patients (Figure 1A). The most sensitive individual test for detection of APS was HPPNA at 52%. This test also had the second lowest specificity at 66%. aCL-IgA was the least sensitive at 4% ($p<0.0001$ versus HPPNA) while aβ2GPI-IgG was the most specific individual assay at 97% ($p<0.0001$ versus HPPNA). Similar trends were seen when APS comorbidities, such as DVT, PE, and stroke, were separately analyzed in SLE patients (Tables 3–5). Within the SLE patients who developed DVT, PE, or stroke, the complete nine-test panel had the greatest sensitivity: 78%, 77%, and 76%, respectively. HPPNA was the second most sensitive in DVT (56%), PE (55%, and stroke patients (53%).

Among patients with PAPS, the nine-test panel had by far the greatest sensitivity at 69.5%, far exceeding that of the most sensitive individual assay, HPPNA, at 36% ($p<0.0001$; Table 2). The nine-panel test had the highest NPV to rule out for PAPS at 46.5%. Along these lines, the nine-panel test also showed the greatest sensitivity to detect PE, DVT, or stroke (Table 2). In 513 patients with PE, HPPNA was the most sensitive individual test for detecting APS (from 349/513 tested, 144/349 resulted in positive HPPNA (41%). Only 50/513 patients were assessed with all 9 tests; 30/50 had at least one positive result, thus achieving greater sensitivity at 60% ($p<0.0001$ relative to HPPNA). In 583 patients with DVT, HPPNA was also most sensitive for detecting APS; from 485/583 tested, 216/485

(45%) resulted in positive HPPNA relative to all other individual tests ($p<0.01$). Only 47/583 patients were assessed with all 9 tests; 36/47 had a least one positive test (sensitivity: 76.6%; $p<0.0001$ relative to HPPNA). In 739 patients with stroke, PNP was the most sensitive individual test for detecting APS; from 81/739 tested, 26/81 resulted in positive PNP (32%). Only 54/739 patients were evaluated with all 9 tests; 39/54 had a least one positive test (sensitivity: 72%; $p<0.0001$ relative to PNP).When combining patients with DVT, PE, and stroke (Table 2), the complete nine-test panel yielded the greatest sensitivity for detecting PAPS (105/151, 69.5%) relative to the most sensitive individual test, HPPNA (382/1060, 36%; $p<0.0001$). The nine-test panel had similar specificity and PPV but markedly higher NPV at 46% over any individual test ($p<0.0001$). These results indicate that performing the full panel of 9 tests yielded the greatest sensitivity for the detection of APS in all patients with thrombotic events (105/151, 70%) and highest NPV at 46.5% for the exclusion of APS in all three groups of non-SLE patients.

The complete nine-test panel was underutilized both in SLE and non-SLE patients with unexplained thrombotic events. Still, the complete panel was used more often in SLE (550/1633; Figure 1A) than non-SLE patients (191/1835; $\chi^2=277$, $p<0.0001$; Figure 1B). HPPNA was also used more often in SLE (1278/1633; Figure 1A) than non-SLE patients (1100/1835; $\chi^2=134$, $p<0.0001$; Figure 1B). PNP was even more underutilized in non-SLE patients (SLE, 726/1633; non-SLE, 315/1835; $\chi^2=305$, $p<0.0001$; Figure 1). PNP was only pursued in 81/739 patients with stroke, however, this was found to be the most sensitive test to detect APS in this cohort (Table 2). Surprisingly, dRVVT (1466/1633) was used more often than HPPNA in SLE patients (1278/1633; $\chi^2=79$, $p<0.0001$); i.e, dRVVT was not tested in 167 patients, while HPPNA was not tested in 355 patients with SLE (Table 1).

aβ2GPI-IgA was more often found in SLE (13/188; Table 1) than non-SLE subjects with thrombosis (22/867; $\chi^2=9.2$, $p=0.0024$; Table 2). In 5/13 aβ2GPI-IgA-positive SLE patients with thrombotic events, none of the other aPL antibody tests were found to be abnormal; among these 5 patients, one patient also had elevated HPPNA, PNP, and dRVVT and 2 patients also had positive HPPNA (not shown). Likewise, aCL-IgA was more often found in SLE (8/189; Table 1) than non-SLE subjects with thrombosis (7/985; $\chi^2=15.6$, $p<0.0001$; Table 2). In 4/8 aCL-IgA-positive SLE patients with APS, none of the other aPL antibody tests were found to be positive; among these 4 patients, one patient also had elevated HPPNA, PNP, and dRVVT, one patient also had elevated HPPNA and PNP, and one patient also had positive HPPNA (not shown). Overall aβ2GPI-IgA was the only positive test in 2 SLE patients with APS, while aCL-IgA was the only positive test in 1 SLE patient with APS. Interestingly, aβ2GPI-IgA was the only positive test in 9/22 non-SLE patients with thrombotic events. Alternatively, aCL-IgA was the only positive test in 2/7 non-SLE patients with thrombotic events.

DISCUSSION

This study demonstrates that a nine-test panel comprising three lupus anticoagulant assays (HPPNA, dRVVT, and PNP) and measurements of IgG, IgM, and IgA anti-phospholipid antibodies (aβ2GPI-IgG, aβ2GPI-IgM, aβ2GPI-IgA, aCL-IgG, aCL-IgM, aCL-IgA) has the greatest sensitivity to detect aPL both in SLE and PAPS subjects. This is a significant

finding since the utilization of all nine tests will aid in expedient recognition of high risk patients such as those who i) need life-long anticoagulation and ii) meet concurrent diagnosis of SLE. Of note, vast differences exist among specialized hemostasis laboratories with respect to the employment of LAC assays as well as methods and outcomes (14). The International Society on Haemostasis and Thrombosis (ISTH) only recommends the testing of dRVVT and activated partial thromboplastin time (aPTT), which is not mirrored by the guidelines of the British Committee for Standards in Haematology (BCSH) and the Clinical and Laboratory Standards Institute (CLSI). The two latter institutions endorse tests other than dRVVT and aPTT (15). Our study clearly indicates that the HPPNA is by far the most sensitive individual LAC test to detect APS in the presence or absence of concurrent SLE. The only exception was PNP, which was the most sensitive test to detect APS in non-SLE patients with stroke. Otherwise, PNP was the 2nd most sensitive test for detection of APS in all other patient groups. In contrast, dRVVT was less sensitive that HPPNA or PNP in all patient groups tested. These observations clearly advocate for the use of HPPNA as a primary screening test, especially in patients with thrombotic events when life-long anticoagulation may prevent potentially fatal relapses.

The nine-test panel was clearly underutilized both in SLE and non-SLE patients with unexplained thrombotic events. However, the complete panel was used more often in SLE patients than non-SLE patients with unexplained thrombotic events. Surprisingly, dRVVT (1466/1633) was used more often than HPPNA in SLE patients (1278/1633; χ^2=79, p<0.0001); i.e, dRVVT was not tested in 167 patients, while HPPNA was not tested in 355 SLE patients. Our findings indicate that HPPNA should be chosen to screen for aPL. This is consistent with earlier observations that HPPNA is underutilized among the various LAC assays (14).

Our nine-test panel includes aβ2-IgA and aCL-IgA antibody assays that have been eliminated from the 2006 Sydney criteria established for the diagnosis of APS (3). The 2011 ACR classification guidelines only recommend testing for IgA antibodies when IgG and IgM antibodies are absent in a thrombotic patient strongly suspected to have APS (16). These society guidelines are clearly reflected by markedly lower frequency of IgA testing in our SLE and PAPS cohorts. However, these guidelines may be problematic considering that outcomes of aPL testing are often not reported within the 4.9-day average length of hospitalization in the United States (17). Moreover, IgA aPL antibodies were the only positive antibody tests in 21 SLE patients (13 with aβ2-IgA and 8 with aCL-IgA). 18 of these 21 patients also had a positive LAC test result. Among PAPS patients, we also encountered 9 subjects with aβ2GPI-IgA and 2 subjects with aCL-IgA as the only positive tests detecting APS. Although the prevalence of aβ2GPI-IgA and aCL-IgA antibodies was increased in APS patients with concurrent SLE relative those not having SLE, the results clearly support systematic testing of IgA aPL antibodies is patients worked up for SLE and PAPS.

While the HPPNA shows less specificity than dRVVT, it poses as an excellent initial screening assay if one does not wish to obtain the complete panel in low risk patients for reasons of cost-effectiveness. However, we strongly advocate for employing the proposed nine-test panel which also concurs with the notion that all APS patients cannot be reliably

identified by a single diagnostic assay (18). Early detection of patients with high-risk profile should allow prophylactic treatment to prevent clotting events in patients undergoing surgical procedures even if they have no previous history of venous occlusions (19). Furthermore, treatment of APS patients with hydroxychloroquine has been associated with reduced risk of thrombosis {8387, 8466}.

Although this study clearly demonstrates the importance to immediately obtain the complete nine-test panel for the diagnosis of SLE and APS, it has several weaknesses. This retrospective study did not delineate the baseline characteristics of the patients that carry additional risk for thromboembolic events, such as hypertension, hyperlipidemia, diabetes, smoking, use of estrogen-containing oral contraceptives, recent long-distance travel or recent surgery. We also did not evaluate patients with pregnancy loss who are typically not admitted to our hospital but constitute another major morbidity of APS. The study did not formally analyze repeated testing after 12 weeks, as advocated in the Sydney criteria (3), which may only apply to antibody assays not influenced by anticoagulation. Nonetheless, despite the weaknesses, these results establish the importance to perform comprehensive testing, as evidenced by the superior sensitivity of the complete nine-test panel; failure to do so may expose patients to life-threatening but preventable thrombotic events.

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List of Abbreviations:

aCL	anti-cardiolipin antibody
aPL	anti-phospholipid antibody
APS	anti-phospholipid syndrome
aβ2GPI	β2-glycoprotein I antibody
aβ2GPI-IgA	IgA antibody against aβ2GPI
aβ2GPI-IgG	IgG antibody against aβ2GPI
aβ2GPI-IgM	IgM antibody against aβ2GPI
aCL-IgA	IgA antibody against cardiolipin
aCL-IgG	IgG antibody against cardiolipin
aCL-IgM	IgM antibody against cardiolipin
dRVVT	diluted Russell viper venom test
HPPNA	hexagonal phase phospholipid neutralization assay
LAC	lupus anticoagulant

NPV	negative predictive value
PAPS	primary APS
PNP	platelet neutralization procedure
PPV	positive predictive value
SLE	systemic lupus erythematosus

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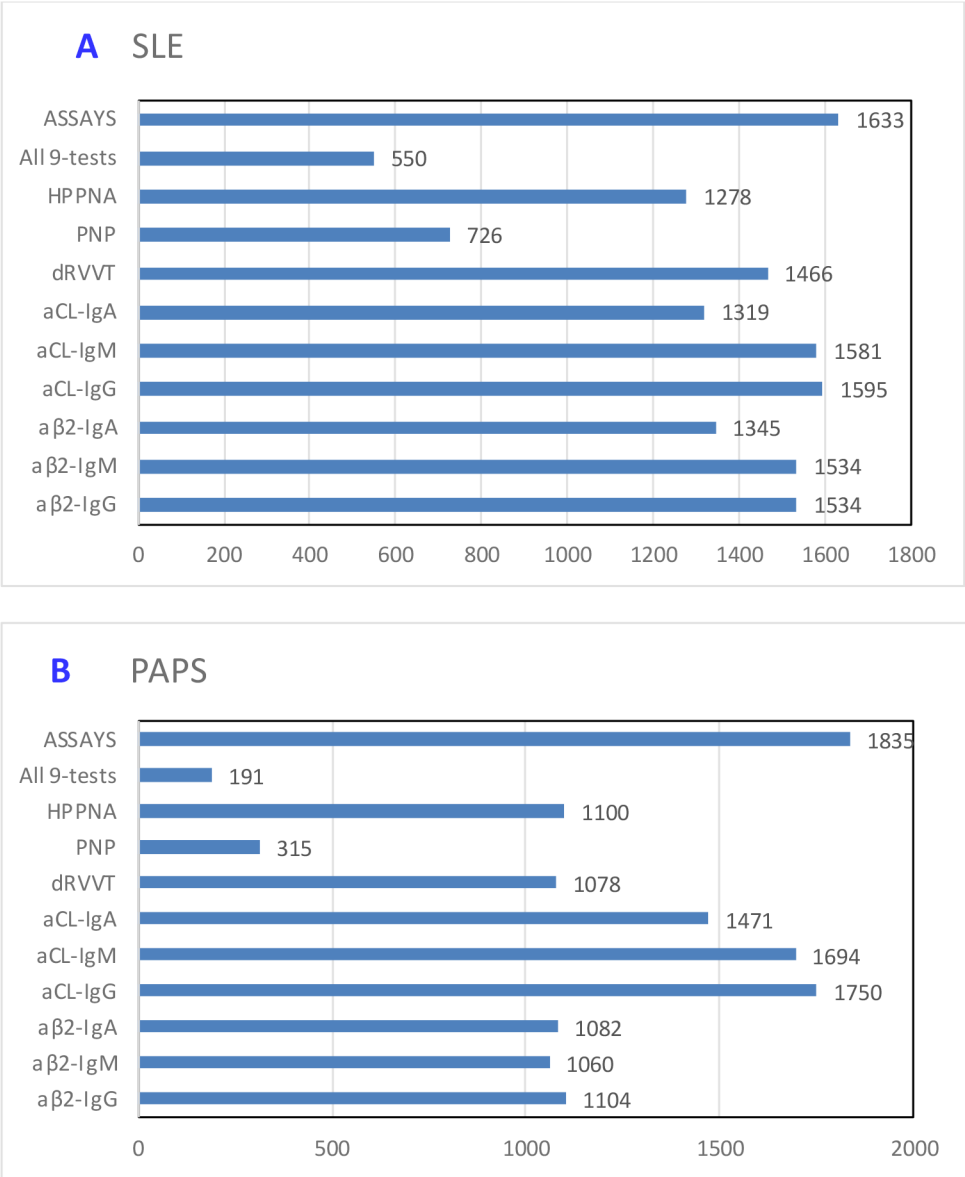

Figure 1.
Frequency of utilization of individual aPL assays and the complete 9-test panel in 1633 SLE patients (panel A) and 1835 PAPS patients (panel B).

Table 1.

Sensitivity and specificity of nine test for detection of APS in SLE patients

TEST	HPPNA	PNP	dRVVT	aβ2GPI-IgG	aβ2GPI-IgM	aβ2GPI-IgA	aCL-IgG	aCL-IgM	aCL-IgA	All tests
APS+ TEST+	102	35	36	15	14	13	21	28	8	73
APS+ TEST−	96	77	155	191	192	175	195	185	181	26
APS−TEST+	395	78	96	43	57	47	81	123	41	215
APS−TEST−	777	536	1179	1285	1271	1110	1298	1245	1089	236
p value	<0.0001	<0.0001	<0.0001	0.0046	NS	NS	0.0316	NS	NS	<0.0001
Sensitivity (%)	52	31	19	7	7	7	10	13	4	74
*p value vs	HPPNA	0.0006	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0003
PPV (%)	21	31	27	26	20	22	21	19	16	25
Specificity (%)	66	87	92	97	96	96	94	91	96	52
*p value vs	HPPNA	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
NPV (%)	89	87	88	87	87	86	87	87	86	90

*p values assessing differences in sensitivity and specificity are compared to HPPNA as a point of reference.

Table 2.

Sensitivity and specificity of nine tests for detection of PAPS in 1835 patients, including 513 with PE, 583 with DVT, and 739 with stroke; all PAPS patients with thrombotic events: HC, healthy controls.

TEST	HPPNA	dRVVT	PNP	aβ2GPI-IgG	aβ2GPI-IgM	aβ2GPI-IgA	aCL-IgG	aCL-IgM	aCL-IgA	TEST
PE TEST+	144	63	20	13	7	3	13	25	2	30
PE TEST−	205	189	45	250	255	194	417	396	250	20
Sensitivity (%)	41	25	30.8	4.9	2.7	1.5	3	5.9	0.8	60
p value vs HPPNA	-	<0.0001	NS	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
DVT TEST+	216	78	40	21	19	9	28	50	2	36
DVT TEST−	269	277	89	411	370	317	569	523	347	11
Sensitivity (%)	44.5	21.97	31	4.9	4.9	2.8	4.7	8.7	0.57	76.6
p value vs HPPNA	-	<0.0001	0.0056	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Stroke TEST+	22	135	26	18	15	10	28	33	3	39
Stroke TEST−	204	296	55	351	354	334	655	627	381	15
Sensitivity (%)	9.7	31.3	32	4.9	4	2.9	4.1	5	0.78	72
p value vs PNP	<0.0001	NS	-	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
PAPS TEST+	382	276	86	52	41	22	69	108	7	105
PAPS TEST−	678	762	189	1012	979	845	1641	1546	978	46
HC TEST+	0	1	0	1	0	7	1	0	0	1
HC TEST−	40	39	40	39	40	208	39	40	486	39
p value	<0.0001	<0.0001	<0.0001	NS	NS	NS	NS	NS	NS	<0.0001
Sensitivity (%)	36.0	26.6	31.3	4.8	4.0	2.5	4.0	6.5	0.7	69.5
p value vs HPPNA	-	<0.0001	NS	<0.0001	0.0006	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
PPV (%)	100	100	100	98	100	76	99	100	100	99
Specificity (%)	100	98	100	98	100	97	98	100	100	98
p value vs HPPNA	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
NPV (%)	5.6	5.0	17.5	3.8	3.9	20.3	23.8	25.2	33.2	46.5

Table 3.

Sensitivity and specificity of nine test for detection of DVT in SLE patients.

TEST	HPPNA	PNP	dRVVT	aβ2-IgG	aβ2-IgM	aβ2-IgA	aCL-IgG	aCL-IgM	aCL-IgA	All tests
DVT+ TEST+	56	18	15	9	9	7	8	14	1	43
DVT+TEST−	44	40	79	93	93	88	99	91	96	12
DVT−TEST+	395	78	96	43	57	47	81	123	41	215
DVT−TEST−	777	536	1179	1285	1271	1110	1298	1245	1089	236
p value	<0.0001	0.0001	0.0039	0.0037	0.0356	NS	NS	NS	NS	<0.0001
Sensitivity (%)	56	31	16	9	9	7	7	13	1	78
*p value vs	HPPNA	0.0024	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0059
PPV (%)	12	19	14	17	14	13	9	10	2	17
Specificity (%)	66	87	92	97	96	96	94	91	96	52
*p value vs	HPPNA	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
NPV (%)	95	93	94	93	93	93	93	93	92	95

*p values assessing differences in sensitivity and specificity are compared to HPPNA as a point of reference.

Table 4.

Sensitivity and specificity of nine test for detection of PE in SLE patients.

TEST	HPPNA	PNP	dRVVT	aβ2-IgG	aβ2-IgM	aβ2-IgA	aCL-IgG	aCL-IgM	aCL-IgA	All tests
PE+ TEST+	29	8	10	3	3	2	5	7	3	23
PE+ TEST−	24	22	42	54	54	52	56	53	52	7
PE− TEST+	395	78	96	43	57	47	81	123	41	215
PE− TEST−	777	536	1179	1285	1271	1110	1298	1245	1089	236
p value	0.0017	0.0281	0.0023	NS	NS	NS	NS	NS	NS	0.0021
Sensitivity (%)	55	27	19	5	5	4	8	12	5	77
*p value vs	HPPNA	0.0135	0.0002	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.04
PPV (%)	7	9	9	7	5	4	6	5	7	10
Specificity (%)	66	87	92	97	96	96	94	91	96	52
*p value vs	HPPNA	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
NPV (%)	97	96	97	96	96	96	96	96	95	97

*p values assessing differences in sensitivity and specificity are compared to HPPNA as a point of reference.

Table 5.

Sensitivity and specificity of nine test for detection of stroke in SLE patients.

TEST	HPPNA	PNP	dRVVT	aβ2-IgG	aβ2-IgM	aβ2-IgA	aCL-IgG	aCL-IgM	aCL-IgA	All tests
Stoke+ TEST+	51	22	18	8	6	10	15	13	5	37
Stoke+ TEST−	45	37	75	89	91	78	86	87	82	12
Stroke− TEST+	395	78	96	43	57	47	81	123	41	215
Stroke-−TEST−	777	536	1179	1285	1271	1110	1298	1245	1089	236
p value	<0.0001	<0.0001	<0.0001	NS	NS	0.0016	0.0004	NS	NS	0.0002
Sensitivity (%)	53	37	19	8	6	11	15	13	6	76
*p value vs	HPPNA	NS	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.009
PPV (%)	11	22	16	16	10	18	16	10	11	15
Specificity (%)	66	87	92	97	96	96	94	91	96	52
*p value vs	HPPNA	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
NPV (%)	95	94	94	94	93	93	94	93	93	95

*p values assessing differences in sensitivity and specificity are compared to HPPNA as a point of reference.