

## Should aPS/PT Be Incorporated into the Routine Serological Tests in the Diagnosis of Antiphospholipid Syndrome?

To the Editor:

We read with great interest the article by Zohoury, *et al*<sup>1</sup> on how to close the serological gap in the diagnosis of antiphospholipid syndrome (APS) by using non-criteria antiphospholipid antibodies (aPL). In their well-designed study, the authors found that using 4 of 11 non-criteria tests [antiphosphatidylserine/prothrombin complex (aPS/PT), antiphosphatidylserine (aPS), antiphosphatidylethanolamine antibodies, and anticardiolipin (aCL)/vimentin antibodies], an accumulative 30.9% of seronegative APS (SN-APS) patients were detected, and there was a further 5.9% increase when using the other 7 non-criteria tests. On the basis of their findings, the authors concluded that patients displaying clinical features of APS but negative for conventional criteria markers should undergo additional testing for non-criteria biomarkers.

Among those non-criteria biomarkers, aPS/PT has exhibited the most promising potential owing to the availability of the well-characterized and standardized commercial ELISA kits<sup>2</sup>. In this letter, we hope to contribute to this discussion by calling attention to an additional report that we recently published on the clinical relevance of aPS/PT in Chinese patients with APS<sup>3</sup>.

In our study, sera from 441 subjects were analyzed, including sera from 101 patients with primary APS (PAPS), 140 patients with secondary APS (SAPS), 34 patients with non-APS thrombosis, 49 patients with non-APS pregnancy-related morbidity, 78 patients with systemic lupus erythematosus, and 39 healthy controls. Among the 241 patients with APS, 31 patients were SN-APS, as suggested by other studies<sup>4</sup>. Those patients fulfilled the clinical criteria for APS, but were negative for the 3 traditional aPL [lupus anticoagulant (LAC), IgG/IgM aCL, and IgG/IgM anti- $\beta_2$ -glycoprotein I (anti- $\beta_2$ -GPI)]<sup>5</sup>. Study protocols were reviewed and approved by the Ethics Committee of Peking Union Medical College Hospital and informed consent was obtained from all participants. Serum aCL (IgG and IgM), anti- $\beta_2$ -GPI (IgG and IgM), and aPS/PT (IgG and IgM) were determined by ELISA (QUANTA Lite ELISA, Inova). We found that IgG and IgM aPS/PT were present in 29.7% and 54.5% of PAPS, and 42.1% and 53.6% of SAPS, respectively. In addition, IgG aPS/PT correlated with venous thrombosis.

Importantly, IgM/IgG aPS/PT were detected in 22.6% of SN-APS (13.3% in SN-PAPS and 31.3% in SN-SAPS), a proportion higher than the results of Zohoury, *et al*<sup>1</sup>. Interestingly, 2 recent studies from China<sup>6,7</sup> also showed the presence of IgM/IgG aPS/PT in SN-APS. One study reported that IgM/IgG aPS/PT were detected in 20% of SN-APS<sup>6</sup>, while the other study indicated that IgM/IgG aPS/PT were present in 51% of SN-APS<sup>7</sup>. In addition to the results from China, data from Europe<sup>1,4</sup> also reported the existence of IgM/IgG aPS/PT in SN-APS, ranging from 9.4% (12/128)<sup>4</sup> to 11.8% (8/68)<sup>1</sup>, further highlighting that IgM/IgG aPS/PT may enhance the diagnostic performance of traditional aPL panel for APS.

As a supplement to our previous study<sup>3</sup>, we further assessed the added value provided by IgM/IgG aPS/PT regarding the APS standard laboratory diagnostic panel<sup>5</sup>. As shown in Table 1, we found that the combination of IgM/IgG aPS/PT with LAC displayed a sensitivity of 52.70%, a specificity of 99.40%, and an LR+ value of 84.84 in the diagnosis of APS, higher than those from the combinations of IgM/IgG aCL with LAC and IgM/IgG anti- $\beta_2$ -GPI with LAC. Importantly, the combination of IgM/IgG aPS/PT with IgM/IgG aCL and LAC resulted in a sensitivity of 38.60% and a specificity of 100%. In addition, the combination of IgG aPS/PT with IgG anti- $\beta_2$ -GPI and LAC exhibited a better correlation with arterial thrombosis than other aPL combinations (Figure 1).

We agree with the conclusions presented by Zohoury, *et al*<sup>1</sup> that the non-criteria biomarkers should be tested in patients displaying clinical features of APS but negative for conventional criteria markers, a practice also suggested by the 2010 International APS Congress<sup>8</sup>. However, the question we emphasize in this letter is whether we should consider incorporating aPS/PT into the routine serological tests in the diagnosis of APS. First, when the 2006 international consensus statement<sup>5</sup> was proposed, the detection of aPS/PT was mainly based on in-house ELISA, resulting in large variability among different studies. Over the past 10 years, the performance of ELISA-based systems for detection of aPS/PT has substantially improved, and commercially available assays with improved sensitivity and specificity have been evaluated in many studies. Second, aPS/PT covers a significant proportion of SN-APS, and the combination of aPS/PT with traditional aPL further enhances the diagnostic power. Third, the introduction of aPS/PT further strengthens risk stratification in patients with APS. Our updated knowledge in aPL and the development of new assays keep moving the field

Table 1. The predictive power of combination of various aPL in the diagnosis of APS. Except for likelihood ratios (LR), data are percentages.

	Sensitivity	Specificity	PPV	NPV	LR+	LR-
aPT/PS IgG or IgM or LAC	79.70	79.50	85.30	72.30	3.89	0.26
aPT/PS IgG or IgM or aCL IgG or IgM	78.80	77.00	83.70	70.90	3.43	0.27
aPT/PS IgG or IgM or anti- $\beta_2$ -GPI IgG or IgM	73.40	79.50	84.30	66.70	3.58	0.33
LAC or aCL IgG or IgM or anti- $\beta_2$ -GPI IgG or IgM	84.20	84.50	89.00	78.20	5.42	0.19
LAC or aCL IgG or IgM or anti- $\beta_2$ -GPI IgG or IgM or aPT/PS IgG or IgM	87.10	71.40	82.00	78.80	3.05	0.18
aPT/PS IgG or IgM and LAC	52.70	99.40	99.20	58.40	84.84	0.48
aPT/PS IgG or IgM and aCL IgG or IgM	46.90	98.10	97.40	55.20	25.16	0.54
aPT/PS IgG or IgM and anti- $\beta_2$ -GPI IgG or IgM	29.90	98.80	97.30	48.50	24.05	0.71
aCL IgG or IgM and LAC	46.90	99.40	99.10	55.60	75.49	0.53
anti- $\beta_2$ -GPI IgG or IgM and LAC	30.70	98.80	97.40	48.80	24.72	0.70
LAC and aCL IgG or IgM and aPT/PS IgG or IgM	38.60	100.00	100.00	52.10	NA	0.61
LAC and aCL IgG or IgM and anti- $\beta_2$ -GPI IgG or IgM	29.50	99.40	98.60	48.50	47.43	0.71
LAC and aCL IgG or IgM and anti- $\beta_2$ -GPI IgG or IgM and aPT/PS IgG or IgM	23.20	100.00	100.00	46.50	NA	0.77

aPL: antiphospholipid antibodies; APS: antiphospholipid syndrome; PPV: positive predictive value; NPV: negative predictive value; NA: not applicable; aPT/PS: antiphosphatidylserine/prothrombin antibodies; aCL: anticardiolipin antibodies; anti- $\beta_2$ -GPI: anti- $\beta_2$ -glycoprotein I; LAC: lupus anticoagulants.

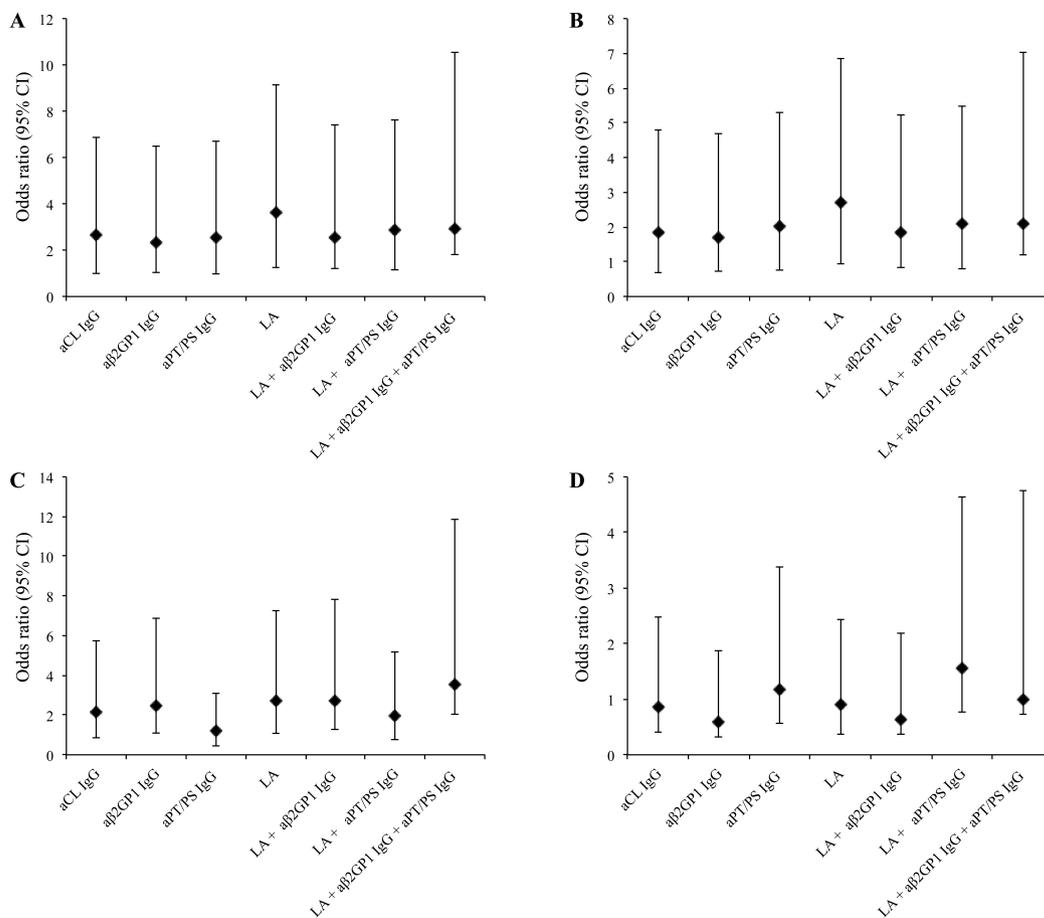


Figure 1. Correlations between multiple aPL and thrombosis (A), venous thrombosis (B), arterial thrombosis (C), and obstetrical complications (D). aPL: antiphospholipid antibodies; aPT/PS: antiprothrombin/antiphosphatidylserine antibodies; aCL: anticardiolipin antibodies; aβ2GPI: anti-β<sub>2</sub>-glycoprotein I; LA: lupus anticoagulants.

forward for both patients and clinicians in the clinical and therapeutic decision-making process.

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