## O29 DETERMINATION OF HOMOGENOUS SUBGROUPS OF ANTIPHOSPHOLIPID SYNDROME: CLUSTER ANALYSIS BASED ON 509 CASES

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**Background** Antiphospholipid syndrome (APS) is a heterogeneous disease, with different phenotypes which may widely vary from classical thrombotic or obstetrical manifestations to catastrophic antiphospholipid syndrome (CAPS). APS can be associated with other auto-immune diseases, such as systemic lupus erythematosus (SLE). We aimed to determine distinct homogenous phenotypes among APS patients, using a non-supervised hierarchical cluster analysis.

**Methods** We performed an observational, retrospective study on APS patients satisfying Sydney classification criteria and enrolled in the French multicentre 'APS and SLE' registry. The clustering process involved an unsupervised multiple correspondence analysis followed by hierarchical ascendant clustering analysis, using 27 selected variables to widely cover APS

**Abstract O29 Table 1** Main characteristics according to devised cluster (N=509)

| | N available data | Cluster 1 | Cluster 2 | Cluster 3 | Cluster 4 | *P* |
|---|---|---|---|---|---|---|
| ***N*** | **509** | **181** | **130** | **102** | **96** | |
| ***Demographic*** | | | | | | |
| Age, *mean (SD)* | 509 | 34.4 (13.3) | **45.8 (15.0)** | 30.7 (12.6) | 33.1 (13.1) | <0.001 |
| Gender, female | 509 | 149 (82.3) | **84 (64.6)** | 94 (92.2) | 69 (71.9) | <0.001 |
| ***Classification criteria*** | | | | | | |
| Arterial thrombosis | 509 | 10 (5.5) | **115 (88.5)** | 21 (20.6) | 66 (68.8) | <0.001 |
| Venous thrombosis | **509** | **141 (77.9)** | 25 (19.2) | **75 (73.5)** | 41 (42.7) | <0.001 |
| Small vessel thrombosis (biopsy proven) | 509 | 3 (1.7) | 1 (0.8) | 2 (2.0) | **30 (31.2)** | <0.001 |
| Pregnancy morbidity¶ | 396 | 55 (29.1) | 10 (11.9) | **34 (36.2)** | **25 (36.2)** | <0.001 |
| ≥1 foetal death >10 wg¶ | 396 | 24 (16.1) | 5 (6.0) | **27 (28.7)** | 15 (21.7) | <0.001 |
| ≥1 premature birth <34 wg due to eclampsia, PE or placental insufficiency¶ | 396 | **21 (14.1)** | 4 (4.8) | 6 (6.4) | 9 (13.0) | 0.037 |
| ≥3 consecutive foetal losses <10 wg¶ | 396 | 13 (8.7) | 2 (2.4) | 2 (2.1) | 4 (5.8) | 0.053 |
| ***Associated manifestations*** | | | | | | |
| CAPS | 509 | 10 (5.5) | 3 (2.3) | 3 (2.9) | **74 (77.1)** | <0.001 |
| APS-associated nephropathy | 494 | 2 (1.1) | 4 (3.2) | 7 (7.0) | **88 (92.6)** | <0.001 |
| Renal hypertension | 480 | 0 (0.0) | 2 (1.6) | 3 (3.0) | **51 (61.4)** | <0.001 |
| Livedo reticularis | 488 | 10 (5.7) | **44 (35.2)** | 18 (18.8) | **33 (35.9)** | <0.001 |
| Seizures | 486 | 2 (1.1) | 10 (8.0) | 8 (8.4) | **13 (14.3)** | 0.001 |
| Migraine | 486 | 10 (5.7) | **26 (20.8)** | 9 (9.5) | 10 (11.0) | 0.001 |
| Chorea | 486 | 0 (0.0) | 1 (0.8) | 1 (1.1) | **4 (4.4)** | 0.020 |
| Valvular involvement | 490 | 0 (0.0) | **26 (21.1)** | 7 (7.2) | **41 (43.6)** | <0.001 |
| ***Associated diseases*** | | | | | | |
| SLE | 509 | 1 (0.6) | 7 (5.4) | **78 (76.5)** | 37 (38.5) | <0.001 |
| Other autoimmune disease* | 509 | 4 (2.2) | 12 (9.2) | **31 (30.4)** | 8 (8.3) | <0.001 |
| Arterial hypertension | 487 | 14 (8.0) | **60 (48.8)** | 11 (11.2) | **45 (49.5)** | <0.001 |
| Diabetes mellitus | 486 | 4 (2.3) | **22 (17.7)** | 1 (1.0) | 5 (5.5) | <0.001 |
| Dyslipidaemia | 485 | 12 (6.9) | **65 (52.4)** | 12 (12.2) | 11 (12.4) | <0.001 |
| ***Biology*** | | | | | | |
| Haemolytic anaemia | 486 | 1 (0.6) | 2 (1.7) | **13 (13.5)** | 7 (7.8) | <0.001 |
| Lymphopenia | 480 | 5 (2.9) | 7 (5.8) | **22 (22.9)** | 2 (2.2) | <0.001 |
| Thrombocytopenia | 490 | 17 (9.7) | 25 (20.5) | **47 (48.0)** | **43 (45.7)** | <0.001 |
| Lupus anticoagulant | 509 | 128 (70.7) | 85 (65.4) | **86 (84.3)** | **84 (87.5)** | <0.001 |
| Anticardiolipin antibodies | 509 | 134 (74.0) | 100 (76.9) | 82 (80.4) | **92 (95.8)** | <0.001 |
| Anti-β2-GPI antibodies | 509 | 114 (63.0) | 86 (66.2) | 53 (52.0) | **70 (72.9)** | 0.019 |
| Triple positivity | 509 | 77 (42.5) | 53 (40.8) | 46 (45.1) | **63 (65.6)** | 0.001 |
| ANA | 432 | 71 (51.1) | 63 (59.4) | **98 (98.0)** | 71 (81.6) | <0.001 |
| Low C3 | 286 | 8 (9.3) | 15 (21.1) | **51 (65.4)** | 28 (54.9) | <0.001 |

Data are expressed as number (% of available data) unless stated otherwise.
Comparisons between different subgroups were performed with Chi-2 tests and ANOVAs.
¶Percentage of obstetrical manifestations were calculated among women only.
*Other autoimmune diseases included Sjögren syndrome, systemic sclerosis, rheumatoid arthritis, or chronic lymphocytic thyroiditis.
Abbreviations: N=number; wg=weeks of gestation; PE=preeclampsia; SLE=systemic lupus erythematosus; ANA=anti-nuclear antibody.

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clinical and biological manifestations. Comparisons between different subgroups were performed with Chi-2 tests and ANOVAs.

**Results** We included 509 patients in the analyses, mainly women (78%). Mean (± SD) age at APS diagnosis was 36.3 ± 14.7 years, and mean follow-up duration after APS diagnosis was 10.3 ± 8.5 years. Cluster hierarchical classification yield in four homogenous groups of patients. Their main characteristics are described in *Table 1*.

1. Cluster 1 (n=181) included mostly patients with venous thrombosis (78%) and premature births due to placenta insufficiency (14%) history, without associated auto–immune disease (only 2.2%).
2. Cluster 2 (n=130) included older patients (mean 45.8 years), less frequently women (65% of women), with arterial events history (89%). Valvular involvement (21%), migraine (21%), livedo (35%), arterial hypertension (49%), and cardiovascular risk factors were relatively frequent.
3. Cluster 3 (n=102) included younger patients, frequently women (mean 30.7 years; 92% women), with associated SLE (76%) or other autoimmune diseases (30%). They frequently had history of venous thrombosis (74%) and of pregnancy morbidity (36%). Thrombocytopenia (48%), haemolytic anaemia (14%), and lupus anticoagulant (84%) were frequent.
4. Cluster 4 (n=96) included mainly patients with a history of CAPS (77%) and/or APS–associated nephropathy (93%), and pregnancy morbidity (36%). Renal hypertension (61%), livedo (36%), seizures (14%), valvular involvement (44%) and triple positivity (66%) were relatively frequent.

**Conclusions** Using an unsupervised clustering method, our study highlighted four distinct homogenous subgroups of APS patients that were predominantly venous; arterial; associated with SLE or other autoimmune disease; and microthrombotic. It confirms the underlying idea of heterogeneous pathophysiological mechanisms.

## O30 COMPLEMENT DEPOSITION, C4D, ON PLATELETS IS ASSOCIATED WITH VASCULAR EVENTS AND ANTIPHOSPHOLIPID ANTIBODIES IN SYSTEMIC LUPUS ERYTHEMATOSUS

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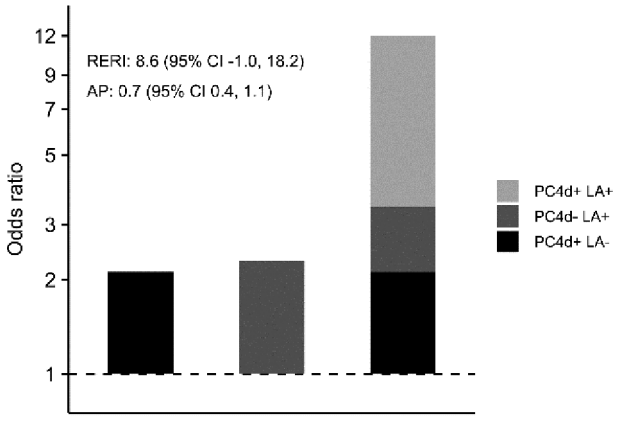
**Objective** Complement components, including C4d, can be found on activated platelets, a process associated with vascular disease in systemic lupus erythematosus (SLE). We investigated whether platelet C4d (PC4d) adds additional value to traditional and known lupus-associated risk factors when identifying SLE patients with vascular disease.

**Method** This cross-sectional study, included 308 well-characterized SLE patients and 308 matched general population controls. PC4d deposition was analyzed using flow cytometry. Values >95% of controls were considered as PC4d positive (+). Antiphospholipid antibodies (aPL) were determined by Luminex, and the lupus anticoagulant (LA) test was performed by the DRVVT test. History of vascular disease (composite and as separate outcomes) was defined at inclusion.

**Results** SLE patients had increased PC4d deposition as compared to population controls (50% versus 5%, p<0.0001). PC4d+ positively associated with any vascular events, and separately with venous and cerebrovascular events, and also with all investigated aPL profiles. The association for any vascular event remained statistically significant after adjustment for traditional and SLE-associated risk factors (OR:2.4, 95% CI 1.3–4.6, p=0.006). Compared to patients negative for both PC4d and LA, patients with double positivity were more likely to have vascular disease (OR:12.0, 95% CI 5.4–28.3; attributable proportion due to interaction 0.7, 95% CI 0.4–1.1) (figure 1).




**Abstract O30 Figure 1 Interaction analysis between PC4d and Lupus Anticoagulant** Interaction between complement C4d deposition (PC4d) and lupus anticoagulant (LA), after adjustment for age (in 10 years), sex, hypertension, estimated glomerular filstration rate (eGFR) according to Modification of Diet in renal Disease (MDRD, per 10 units), and smoking, on the odds of vascular disease (arterial and/or venous) in individuals with systemic lupus erythematosus. RERI = relative excess risk due to interaction; AP = attributable proportion due to interaction. See supplementary material for figures.

**Conclusions** PC4d+ is associated with vascular events in SLE, independently of traditional and SLE-associated risk factors. Concurrent presence of PC4d and LA seem to interact to further increase the odds for vascular events. Prospective studies should examine whether the aPL/PC4d combination can improve prediction of vascular events in SLE and/or APS.

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