**Morbidity and mortality in antiphospholipid syndrome based on cluster analysis: a 10-year longitudinal cohort study**

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Conflict of interest

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**Keywords**

Antiphospholipid syndrome (APS), morbidity, mortality, cardiovascular risks, history of arterial thrombosis, cluster analysis

**Abstract**

OBJECTIVE: To identify a group with poor prognosis and clarify its characteristics among patients with antiphospholipid syndrome (APS) using cluster analysis.

METHODS: This is a longitudinal retrospective cohort study of APS patients. Cluster analysis was performed to classify the patients using clinical data and the profile of antiphospholipid antibody (aPL). Events were defined as thrombosis, severe bleeding, and mortality.

RESULTS: A total of 168 APS patients were included. Cluster analysis classified the patients into three groups; Cluster A (n=61): secondary APS, Cluster B (n=56): accumulation of cardiovascular risks and arterial thrombosis, Cluster C (n=61): triple positivity of aPL and venous thrombosis. Cluster B showed significantly high frequency of the events and high mortality compared with the other clusters (P = 0.0112 for B vs. A and P=0.0471 for B vs. C).

CONCLUSION: Using cluster analysis, we clarified the characteristics of APS patients with poor prognosis. Risk factors for cardiovascular disease may further increase events in APS patients.

## Introduction

Antiphospholipid syndrome (APS) is an autoimmune disease characterized by thrombotic events and pregnancy complications associated with persistently positive antiphospholipid antibodies (aPL) (1), including lupus anticoagulant (LA), anti-cardiolipin antibodies (aCL) and anti-β2GlycoproteinIantibodies (aβ2GPI). Other non-criteria aPL, particularly phosphatidylserine-dependent anti-prothrombin antibodies (aPS/PT) and antibodies against domain I of β2GPI have also been reported to be related with APS manifestations (2). The persistent presence of aPL represents a thrombotic risk in APS which can be stratified according to the aPL profile (3).

APS patients with high-risk aPL profile have a high rate of thrombotic recurrences regardless of antithrombotic therapy (4). In the European League Against Rheumatism (EULAR) recommendations for the management of APS, high-risk aPL profiles were defined as the presence of LA, the presence of double or triple aPL positivity, or the presence of persistently high aPL titres (3).

To assess the thrombotic risk in APS, aPL score (aPL-S) and Global APS score (GAPSS) were developed. The aPL-S is a quantitative marker that represents the

individual aPL profile and aPL-S ≧30 is a considerable risk factor for the development of thrombosis (5). GAPSS is a tool to calculate the relative risk of each aPL for vascular thrombosis or pregnancy morbidity. GAPSS >16 has been reported as an independent risk factor for future thrombotic events (6). However, a prognosis assessment with the risk stratification has not yet been reported in patients with APS. The characteristics of APS patients in addition to the aPL profile might contribute to the poor outcomes. Accordingly, adequate prognosis assessment should be established in patients with APS using the integrate information including aPL profile, clinical information and complications.

Cluster analysis is a statistical method that identifies subgroups as defined by multiple characteristics. Recently, cluster analysis has been applied to identified clinical and laboratory characteristics in patients with APS (7) . The subgroups of patients are determined by a hierarchical cluster analysis from the multiple correspondence according to clinical and laboratory characteristics. The use of cluster analysis could visualise the accurate categorisation to evaluate the prognosis.

In this study, we aim to identify the group with the poor prognosis in Japanese patients diagnosed with APS based on cluster analysis.

## Methods

### Patients and methods

This retrospective study has been conducted in a single centre at Hokkaido University Hospital in Sapporo, and in accordance with ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines approved by Hokkaido University Hospital ethics committee (approval number: 017-0354).

The study included patients diagnosed with APS between April 1990 and May 2019 according to the Sydney revised Sapporo criteria for definite APS (8). Medical reports were carefully retrospectively reviewed and clinical/laboratory data extracted. The coexistence of systemic lupus erythematosus (SLE) was diagnosed according to the American College of Rheumatology (ACR) revised criteria (9). All treating physicians were board-certified rheumatologists by the Japan College of Rheumatology, and the therapeutic regimen administered following the corresponding APS guidelines. Patients

who were followed-up for less than 2 years were excluded. Risk factors for arterial thrombosis including hypertension, diabetes mellitus, dyslipidaemia and smoking were recorded at the start of the observation period. Cardiovascular risks included hypertension, dyslipidaemia, diabetes mellitus, smoking and the aPL-S ≧ 30.

**Antiphospholipid antibody testing**

IgG and/or IgM aCL(10), IgG and/or IgM aβ2GPI (11), IgG and/or IgM aPS/PT(12) were evaluated by enzyme-linked immunosorbent assay as described previously. For the detection of LA, the guidelines recommended by the Subcommittee for Standardization of the International Society on Thrombosis and Haemostasis were followed (13) . Antiphospholipid antibodies were assayed in all the patients at the first visit to the autoimmune outpatient clinic and at least a second time, separated by at least twelve weeks. Triple positive aPL was defined according to a previous report(3) as positive for LA, IgG/IgM aCL and IgG/IgM aβ2GPI.

**Cluster analysis**

We applied a hierarchical cluster analysis at the time of diagnosis. We determined APS patients aggregating into different groups sharing common characteristics using the following variables : age at APS onset, aPL-S, sex, SLE, hypertension, dyslipidaemia, diabetes mellitus, three or more cardiovascular risks, history of arterial thrombosis, history of venous thrombosis, positivity for LA, IgG/IgM aCL, IgG/IgM aβ2GPI and/or IgG/IgM aPS/PT. Euclidean distance and the Ward agglomerative method were applied. Each variable is considered as a single cluster and combined with a neighbouring variable determined by the Euclidean distance. A dendrogram showed the process of clustering and the distance between the cluster. To identify the ideal number of clusters, we decided to three clusters with reference to the dendrogram (Supplement Figure1A and 1B). Kaplan-Meier analysis and multiple comparisons were performed in these clusters.

**Endpoints**

The endpoint was set as event-free survival. The event was defined as thrombosis in either arterial or venous territories, severe bleeding events or death. The observation

period of each patient was established as the baseline when diagnosed with APS, and to end either at the time of an event or at the end of the observation. The presence of thrombosis was confirmed by imaging studies, and severe bleeding was defined as bleeding episodes that required hospitalisation and/or blood transfusion.

**Statistical analysis**

Categorical variables were described as counts and percentages. Continuous variables were expressed as median and quartiles. Fisher exact test was used for qualitative data analysis. Multiple comparisons were analysed by Kruskal-Wallis test. Kaplan-Meier curves were applied to estimate the rates of mortality and events. In all statistical analyses, $p < 0.05$ was taken to indicate statistical significance. All statistical analyses were performed using JMP® Pro 14.2.0 (SAS Institute Inc., Cary, North Carolina, USA).

**Results**

**Baseline Characteristics of each cluster**

A total of 168 APS patients were recruited. Demographic, clinical and laboratory data from all patients are summarised in Table 1. The cohort comprised 144 females and 24 males, median age at disease onset was 39 (range 29.5-55) years old and the median observation periods 10 (5-15) years. Cluster analysis classified the 168 patients into three groups.

**Cluster A: secondary APS**

Cluster A included 61 patients (36 % of the total cohort) and 72% of patients had SLE. The median observation period was 8 years. One death (1.6 %) and 16 events (26 %) occurred during the observation period. Cluster A was categorized as a secondary APS group.

**Cluster B: accumulation of cardiovascular risks and arterial thrombosis**

Cluster B included 56 patients (33.3 % of the total cohort) older than those in other groups. These patients had the highest rate of cardiovascular risks, such as hypertension, dyslipidaemia diabetes mellitus. The characteristics of this cluster was the high

prevalence of arterial thrombosis. The median observation period was 9 years. Eight deaths (14 %) and 28 events (50 %) occurred during the observation period. Cluster B was categorised as high-risk thrombosis and arterial thrombosis group.

**Cluster C: triple positive aPL and venous thrombosis**

Cluster C included 51 patients (30.4 % of the total cohort) and these patients had a high rate of triple positive aPL. The median observation period was 14 years. Five deaths (9.8 %) and 21 events (41 %) occurred during the observation periods. Cluster C was categorised as triple positive aPL and venous thrombosis group.

**All events free survival: thrombosis, severe bleeding or death**

The events occurred in 65 patients during the observation period and details of the events are summarized in Table 2. In Kaplan-Meier analysis, 5 and 10-year events free survival rates in APS patients were 81.7 % and 64.7 %, respectively (Figure 1A). In cluster analysis, cluster B had a significantly higher event rate (5.56 per 100 patients-years) than the other clusters (P = 0.0112: log-rank test) (Table2 and Figure 1B).

**Event free survival: thrombosis**

The thrombosis occurred in 47 patients including 37 of arterial thrombosis and 10 of venous thrombosis during the observation period. The rate of thrombosis was 2.8 per 100 patient-years. The Kaplan-Meier analysis of cluster A, B and C showed 10-year survival rates of 75.5%, 62.9% and 83.5%, respectively. There was not any statistically significant difference among the three clusters. (P = 0.119: log-rank test) (Table2 and Figure2A). A subanalysis of arterial and venous thrombosis also showed no differences for developing thrombosis among the three clusters, respectively (arterial thrombosis P=0.10, venous thrombosis P=0.17).

**Event free survival: severe bleeding**

The severe bleeding occurred in 9 patients during the observation period. Severe bleeding rate was 0.54 per 100 patient-years. In Kaplan-Meier analysis of each cluster, 10-year survival rates were 98.3%, 92.2% and 92.3%, respectively. No statistically

significant difference was recorded among the three clusters, (P = 0.142: log-rank test) (Table2 and Figure2B).

**Event free survival: death**

The deaths occurred in 14 patients during the observation period. Mortality was 0.83 per 100 patient-years. Kaplan-Meier analysis revealed 10-year overall survival rates of 100%, 83.2 % and 95.5 %, respectively. In cluster analysis, cluster B had significantly higher mortality compared to the other clusters,1.59 per 100 patients-years, (P = 0.047: log-rank test) (Table 2 and Figure 2C).

**Discussion**

To the best of our knowledge, this retrospective study was the first trial to evaluate the 10-year event-free survival rate of the patients with APS based on cluster analysis. The clustering classified APS patients into three subgroups as follows; “secondary APS” “accumulation of cardiovascular risks and arterial thrombosis” or “triple aPL positive and venous thrombosis”. This clustering was different from that reported previously

159 based on serological data (7). The clustering used in our study combines serological and
160 clinical follow-up data.
161 Cluster B categorised as “accumulation of cardiovascular risks and arterial
162 thrombosis” group. Multiple risk factors for cardiovascular disease including
163 hypertension, dyslipidaemia and diabetes mellitus are recognised as risk factors for
164 thrombosis (14, 15). Cluster B had higher risk of events than cluster A and C, the
165 former having SLE as another thrombotic risk (16, 17) and the latter triple positive aPL
166 (18, 19). In addition, Cluster B showed the highest mortality in parallel with the
167 increased number of the events. The 10-year survival rates in our cohort (92.7%) was
168 similar to that reported in the European APS cohort (90.7%) (2). The major causes of
169 death, as well as the rate of thrombosis and serious bleeding events were similar
170 between two cohorts. The bias related to different ethnic backgrounds might be lower in
171 our study. To exclude age biased, multivariate analysis including age was performed
172 (Supplement Table3). Cox's proportional hazards model confirmed the significance of
173 high rate of events in a three or more cardiovascular risks and arterial thrombosis. Given
174 these evidences, the accumulation of the thrombotic risks would contribute to the higher

175 incidence of events and mortality. It is, hence, important to control these vascular risk
176 factors, especially in APS patients with arterial thrombosis.
177 The primary trigger for arterial thrombosis is the rupture of an atherosclerotic plaque.
178 Antibodies against β2GPI are associated with the autoimmune-mediated
179 atherothrombosis (20). β2GPI binds oxidized low-density lipoproteins (oxLDL) likely
180 to quench the pro-inflammatory and proatherogenic effects of the oxLDL molecule.
181 APS patients have increasing serum levels of oxLDL/ β2GPI complexes (21), leading to
182 the activation of monocytes and tissue factor expression (22). Although the aPL profiles
183 in each cluster were not significant difference in our study, cluster B had three or more
184 cardiovascular risks including dyslipidaemia. Therefore, aPL-mediated atherosclerosis
185 might be related with the poor outcome.
186 We applied cluster analysis to identify a group with poor prognosis in patients with
187 APS. In addition, the cluster analysis can clarify the characteristics of the groups
188 regarding the clinical and laboratory data. The ability to identify cluster–associated
189 outcomes can be useful for the management of heterogeneous diseases. Recently,
190 machine learning techniques such as cluster analysis is employed to ensure that

populations are similar relative to the outcome of interest in clinical trials of novel therapies(23). The cluster analysis may have potential implications for the management of patients with APS.

This study has some limitations. First, due to the study design, a single centre retrospective study, there may be an imbalanced number of patients. Second, the obstetric complication variable was not calculated in the clustering analysis, because males with missing the pregnancy data would affect the clustering analysis. Finally, the treatment variable was excluded in the cluster analysis due to the huge variation among patients.

In conclusion, the cluster analysis revealed three groups of APS patients that were significantly different from each other as either “secondary APS” “accumulation of cardiovascular risks and arterial thrombosis” or “triple aPL positive and venous thrombosis”. The group named as “accumulation of cardiovascular risks and arterial thrombosis” had the poorest prognosis among the three groups, indicating that risk factors for cardiovascular disease may further increase events in APS patients.

206 Treatment strategy based on the risk stratification using cluster analysis would be

207 needed in patients with APS.

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Figure Legends

Figure 1

Cumulative event-free survival curves in APS patients by Kaplan-Meier analysis.

(A) Cumulative event-free survival curves in 168 APS patients. Five-year event-free survival rate was 81.7% and 10-year event-free survival rate was 64.7%.

(B) Cumulative event-free survival curves in the three clusters. Five-year event-free survival rates were 82.4%, 74.9% and 87.9%, respectively. Ten-year event-free survival

rates were 74.2%, 48.1% and 73.1%, respectively. Cluster B had statistically significant high rates of incidence of events. (P = 0.0112: log-rank test)

Cluster A: secondary APS, Cluster B: accumulation of cardiovascular risks and arterial thrombosis, Cluster C: triple antiphospholipid antibody (aPL) positive and venous thrombosis.

Figure 2

Cumulative event-free survival curves in APS patients by Kaplan-Meier analysis.

(A) Cumulative thrombosis-free survival curves in the three clusters. Five-year survival rates were 83.8%, 79.3% and 91.7%, respectively. Ten-year survival rates were 75.5%, 62.9% and 83.5%, respectively. There were not statistically significant differences among the three clusters. (P = 0.119: log-rank test)

(B) Cumulative bleeding-free survival curves in the three clusters. Five-year survival rates were 98.3%, 95.1% and 97.9%, respectively. Ten-year survival rates were 98.3%, 92.2% and 92.3%, respectively. There were not statistically significant differences among

the three clusters. (P = 0.142: log-rank test)

(C) Cumulative survival curves in the 3 clusters. Five-year survival rates were 100%, 95.7% and 98.0%, respectively. Ten-year survival rates were 100%, 83.2% and 95.5%, respectively. There was statistically significant difference among the three clusters. (P = 0.0471: log-rank test)

Cluster A: secondary APS, Cluster B: accumulation of cardiovascular risks and arterial thrombosis, Cluster C: triple antiphospholipid antibody (aPL) positive and venous thrombosis.

Table 1. Characteristics of the APS patients in the 3 clusters (n=168)

| Variable | | All (n=168) | Cluster A (n=61) | Cluster B (n=56) | Cluster C (n=51) | P value |
|---|---|---|---|---|---|---|
| Age (years) | Median (range) | 39 (29.5-55) | 32 (25-38) | 56 (50-63) | 39 (25-51) | < 0.001 |
| Observation time (months) | Median (range) | 10 (5-15) | 8 (3-14) | 9 (5-14) | 14 (7-17) | 0.004 |
| Female | n (%) | 144 (85.7) | 52 (85.2) | 49 (87.5) | 43 (84.3) | 0.890 |
| Primary APS | n (%) | 63 (37.5) | 15 (24.6) | 26 (46.4) | 22 (43.1) | 0.032 |
| APS and SLE | n (%) | 98 (58.3) | 44 (72.1) | 27 (48.2) | 27 (52.9) | 0.031 |
| APS and SS | n (%) | 6 (3.6) | 2 (3.3) | 3 (5.4) | 1 (2.0) | 0.775 |
| APS and MCTD | n (%) | 1 (0.6) | 0 | 1 (1.8) | 0 | 0.637 |
| APS and RA | n (%) | 1 (0.6) | 0 | 1 (1.8) | 0 | 0.637 |
| Hypertension | n (%) | 75 (44.6) | 24 (39.3) | 34 (60.7) | 17 (33.3) | 0.010 |
| Dyslipidemia | n (%) | 64 (38.1) | 16 (26.2) | 28 (50.0) | 20 (39.2) | 0.028 |
| Diabetes mellitus | n (%) | 23 (13.7) | 6 (9.8) | 11 (19.6) | 6 (11.8) | 0.304 |
| Smoking | n (%) | 39 (23.2) | 16 (26.2) | 13 (23.2) | 10 (19.6) | 0.742 |
| History of arterial thrombosis | n (%) | 108 (64.3) | 32 (52.5) | 46 (82.1) | 30 (58.8) | 0.002 |
| Cerebral infarction | n (%) | 92 (54.8) | 25 (41.0) | 39 (69.6) | 28 (54.9) | 0.008 |
| Coronary heart disease | n (%) | 6 (3.6) | 2 (3.3) | 3 (5.4) | 1 (2.0) | 0.775 |
| Arterial ischaemia in legs | n (%) | 5 (3.0) | 3 (4.9) | 1 (1.8) | 1 (2.0) | 0.625 |
| Mesenteric artery occlusion | n (%) | 3 (1.8) | 1 (1.6) | 2 (3.6) | 0 | 0.644 |
| Central retinal artery occlusion | n (%) | 2 (1.2) | 0 | 2 (3.6) | 0 | 0.201 |
| Renal infarction | n (%) | 1 (0.6) | 0 | 0 | 1 (2.0) | 0.304 |
| Aortic thrombosis | n (%) | 1 (0.6) | 1 (1.6) | 0 | 0 | 1.000 |
| History of venous thrombosis | n (%) | 53 (31.5) | 18 (29.5) | 10 (17.9) | 25 (49.0) | 0.003 |
| Deep vein thrombosis | n (%) | 39 (23.2) | 13 (21.3) | 8 (14.3) | 18 (35.3) | 0.035 |
| Pulmonary embolism | n (%) | 17 (10.1) | 7 (11.5) | 2 (3.6) | 8 (15.7) | 0.089 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Central retinal vein occlusion | n (%) | 2 (1.2) | 2 (3.3) | 0 | 0 | 0.331 |
| Superficial thrombophlebitis | n (%) | 2 (1.2) | 0 | 1 (1.8) | 1 (2.0) | 0.535 |
| History of obstetric complications | n (%) | 50 (34.7) | 22 (42.3) | 8 (16.3) | 20 (46.5) | 0.006 |
| Pregnancy-induced hypertension / eclampsia | n (%) | 6 (4.2) | 3 (5.8) | 0 | 3 (7.0) | 0.203 |
| Late fetal loss (≥ 10 weeks) | n (%) | 28 (19.4) | 10 (19.2) | 7 (14.3) | 11 (25.6) | 0.447 |
| Premature birth (< 34 weeks) | n (%) | 4 (2.8) | 0 | 1 (1.9) | 3 (7.0) | 0.072 |
| Recurrent abortions (< 10 weeks) | n (%) | 19 (13.2) | 11 (21.2) | 0 | 8 (18.6) | 0.007 |
| LA | n (%) | 138 (82.1) | 49 (80.3) | 41 (73.2) | 48 (94.1) | 0.011 |
| aCL IgG/IgM | n (%) | 95 (56.5) | 21 (34.4) | 24 (42.9) | 50 (98.0) | < 0.001 |
| aβ2GPI IgG/IgM | n (%) | 99 (58.9) | 26 (42.6) | 25 (44.6) | 48 (94.1) | < 0.001 |
| aPS/PT IgG/IgM | n (%) | 116 (69.0) | 38 (62.3) | 30 (53.6) | 48 (94.1) | < 0.001 |
| Triple positive | n (%) | 65 (38.7) | 7 (11.5) | 12 (21.4) | 46 (90.2) | < 0.001 |
| aPL-S | Mean (SD) | 31.0 (25.0) | 16.8 (12.4) | 20.4 (16.3) | 59.7 (20.2) | < 0.001 |

PAPS: Primary antiphospholipid syndrome, SLE: Systemic lupus erythematosus, SS: Sjögren syndrome, RA: Rheumatoid arthritis, MCTD: Mixed connective tissue disease, aPL-S: antiphospholipid antibody score,

LA: lupus anticoagulant, aCL: anticardiolipin antibody, aβ2GPI: anti-β2Glycoprotein I antibody,

aPS/PT: phosphatidylserine dependent anti-prothrombin antibody

Triple positive: LA, IgG/M aCL and IgG/M aβ2GPI were detected at the same time

P-values <0.05. P-values were calculated using Kruskal-Wallis test or Fisher's Exact Test.

Table 2. Events in APS patients

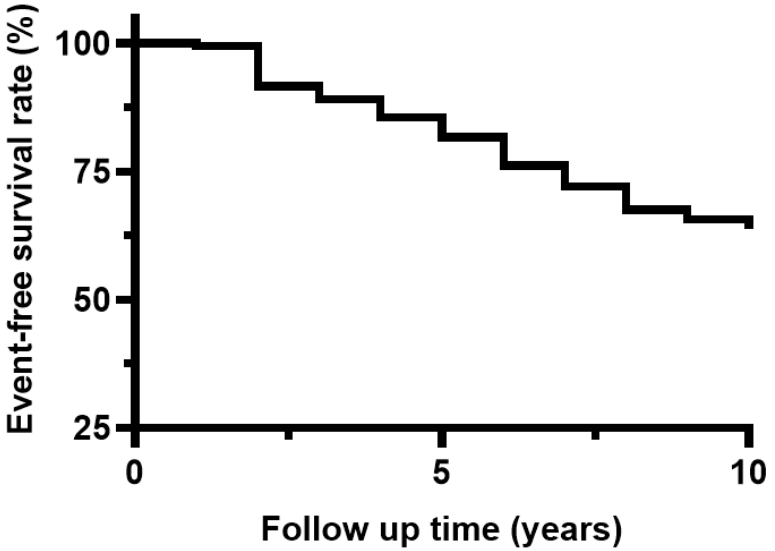
| Variable | | All (n=168) | Cluster A (n=61) | Cluster B (n=56) | Cluster C (n=51) | P value |
|---|---|---|---|---|---|---|
| Events | n (%) | 65 (38.7) | 16 (26.2) | 28 (50.0) | 21 (41.2) | 0.028 |
| Events occur rate per 100 patients-year | patients-year | 3.87 | 3.28 | 5.56 | 2.94 | |
| Thrombosis | n (%) | 47 (28.0) | 14 (23.0) | 19 (33.9) | 14 (27.5) | 0.428 |
| Arterial thrombosis | n (%) | 37 (22.0) | 10 (16.4) | 15 (26.8) | 12 (23.5) | 0.372 |
| Cerebral infarction | n (%) | 32 (19.1) | 7 (11.5) | 14 (25.0) | 11 (21.6) | 0.143 |
| Coronary heart disease | n (%) | 3 (1.8) | 1 (1.6) | 1 (1.8) | 1 (2.0) | 1.000 |
| Central retinal artery occlusion | n (%) | 1 (0.6) | 1 (1.6) | 0 | 0 | 1.000 |
| Arterial ischaemia in legs | n (%) | 1 (0.6) | 1 (1.6) | 0 | 0 | 1.000 |
| Venous thrombosis | n (%) | 10 (6.0) | 4 (6.6) | 4 (7.1) | 2 (3.9) | 0.780 |
| Deep vein thrombosis | n (%) | 8 (4.8) | 4 (6.6) | 2 (3.6) | 2 (3.9) | 0.738 |
| Pulmonary embolism | n (%) | 2 (1.2) | 2 (3.3) | 0 | 0 | 0.331 |
| Central retinal vein occlusion | n (%) | 1 (0.6) | 0 | 1 (1.8) | 0 | 0.637 |
| Superficial thrombophlebitis | n (%) | 1(0.6) | 0 | 1 (1.8) | 0 | 0.637 |
| Recurrence rate per 100 patients-year | patients-year | 2.80 | 2.87 | 3.77 | 1.96 | |
| Severe bleeding events | n (%) | 9 (5.4) | 1 (1.6) | 5 (8.9) | 3 (5.9) | 0.214 |
| Alveolar haemorrhage | n (%) | 1 (0.6) | 0 | 1 (1.8) | 0 | 0.637 |
| Aortic aneurysm rupture | n (%) | 1 (0.6) | 0 | 1 (1.8) | 0 | 0.637 |
| Gastrointestinal haemorrhage | n (%) | 2 (1.2) | 0 | 2 (3.6) | 0 | 0.201 |
| Cerebral haemorrhage | n (%) | 5 (3.0) | 1 (1.6) | 1 (1.8) | 3 (5.9) | 0.445 |
| Severe bleeding rate per 100 patients-year | patients-year | 0.54 | 0.20 | 0.99 | 0.42 | |
| Death | n (%) | 14 (8.3) | 1 (1.6) | 8 (14.3) | 5 (9.8) | 0.030 |
| Related to thrombosis | n (%) | 2 (1.2) | 0 | 1 (1.8) | 1 (2.0) | 0.535 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Cerebral infarction | n (%) | 2 (1.2) | 0 | 1 (1.8) | 1 (2.0) | 0.535 |
| Related to bleeding | n (%) | 2 (1.2) | 0 | 2 (3.6) | 0 | 0.201 |
| Alveolar haemorrhage | n (%) | 1 (0.6) | 0 | 1 (1.8) | 0 | 0.637 |
| Aortic aneurysm rupture | n (%) | 1 (0.6) | 0 | 1 (1.8) | 0 | 0.637 |
| Others | n (%) | 10 (6.0) | 1 (1.6) | 5 (8.9) | 4 (7.8) | 0.158 |
| Intestinal pneumonia | n (%) | 2 (1.2) | 0 | 1 (1.8) | 1 (2.0) | 0.535 |
| SLE activity | n (%) | 1 (0.6) | 1 (1.6) | 0 | 0 | 1.000 |
| Infection/sepsis | n (%) | 1 (0.6) | 0 | 1 (1.8) | 0 | 0.637 |
| Lung cancer | n (%) | 1 (0.6) | 0 | 1 (1.8) | 0 | 0.637 |
| Malignant lymphoma | n (%) | 1 (0.6) | 0 | 1 (1.8) | 0 | 0.637 |
| Amyotrophic lateral sclerosis | n (%) | 1 (0.6) | 0 | 1 (1.8) | 0 | 0.637 |
| Drowning | n (%) | 1 (0.6) | 0 | 0 | 1 (2.0) | 0.304 |
| Unknown | n (%) | 2 (1.2) | 0 | 0 | 2 (3.9) | 0.091 |
| Mortality per 100 patients-year | n (%) | 0.83 | 0.20 | 1.59 | 0.70 | |

APS: Antiphospholipid syndrome, SLE: Systemic lupus erythematosus

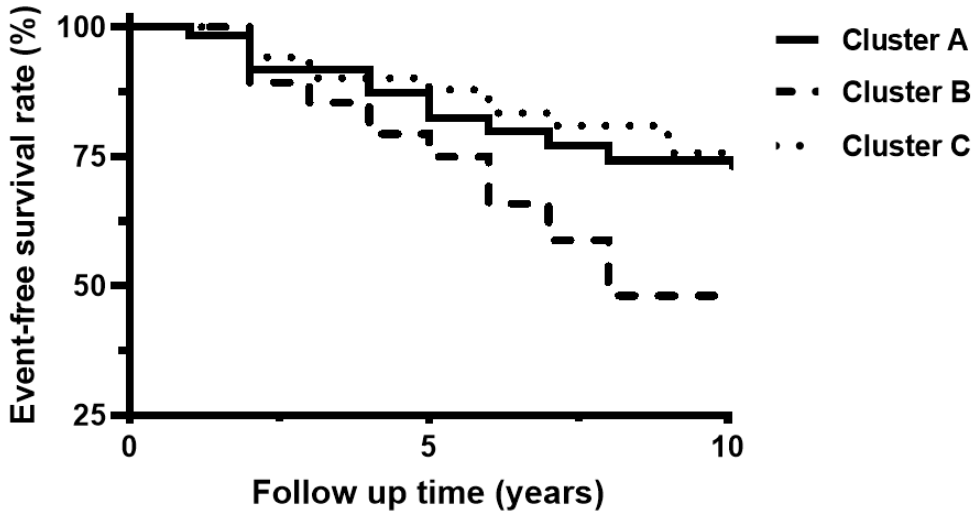
P-values <0.05. P-values were calculated using Kruskal-Wallis test or Fisher's Exact Test.

## Figure 1A (all)



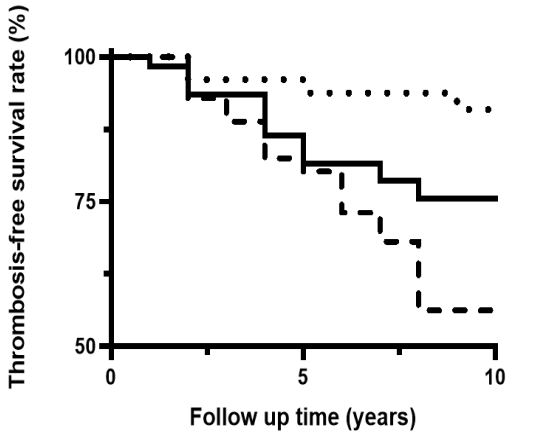

| | | | | | |
|---|---|---|---|---|---|
| N | 168(0) | 140(14) | 112(28) | 81(40) | 67(48) |

## Figure 1B (Cluster)



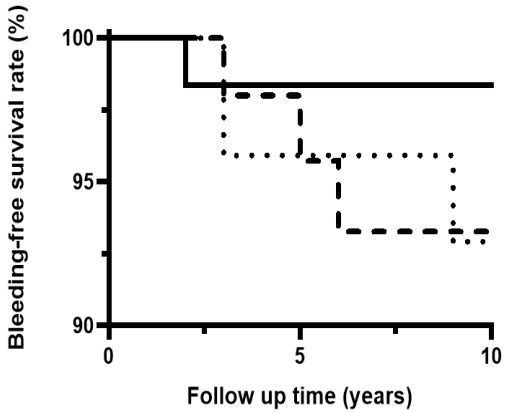

| | | | | | |
|---|---|---|---|---|---|
| Cluster A | 61(0) | 47(5) | 36(9) | 27(10) | 22(13) |
| Cluster B | 56(0) | 46(6) | 36(13) | 22(20) | 16(24) |
| Cluster C | 51(0) | 47(2) | 40(5) | 32(8) | 29(11) |

## Figure 2A
## (Recurrent thrombosis)



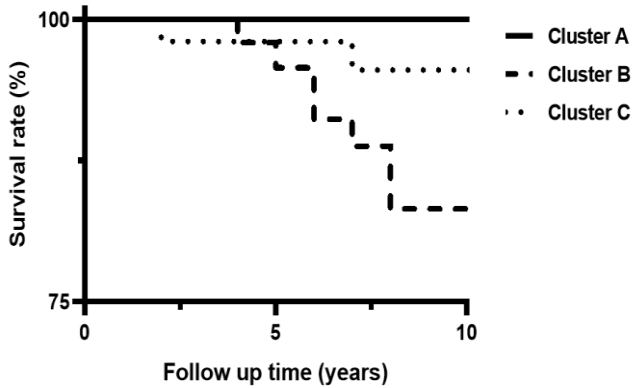

| | | | | | |
|---|---|---|---|---|---|
| Cluster A | 61(0) | 47(4) | 35(9) | 26(10) | 21(11) |
| Cluster B | 56(0) | 46(4) | 36(10) | 23(15) | 17(19) |
| Cluster C | 51(0) | 47(2) | 41(3) | 34(3) | 32(4) |

## Figure 2B
## (Severe Bleeding)




| | | | | | |
|---|---|---|---|---|---|
| Cluster A | 61(0) | 49(1) | 40(1) | 33(1) | 26(1) |
| Cluster B | 56(0) | 50(0) | 43(2) | 31(3) | 26(3) |
| Cluster C | 51(0) | 49(0) | 42(2) | 34(2) | 31(3) |

## Figure 2C
## (Mortality)




| | | | | | |
|---|---|---|---|---|---|
| Cluster A | 61(0) | 49(0) | 40(0) | 33(0) | 26(0) |
| Cluster B | 56(0) | 51(0) | 44(2) | 32(7) | 27(7) |
| Cluster C | 51(0) | 49(1) | 44(2) | 37(2) | 34(2) |