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

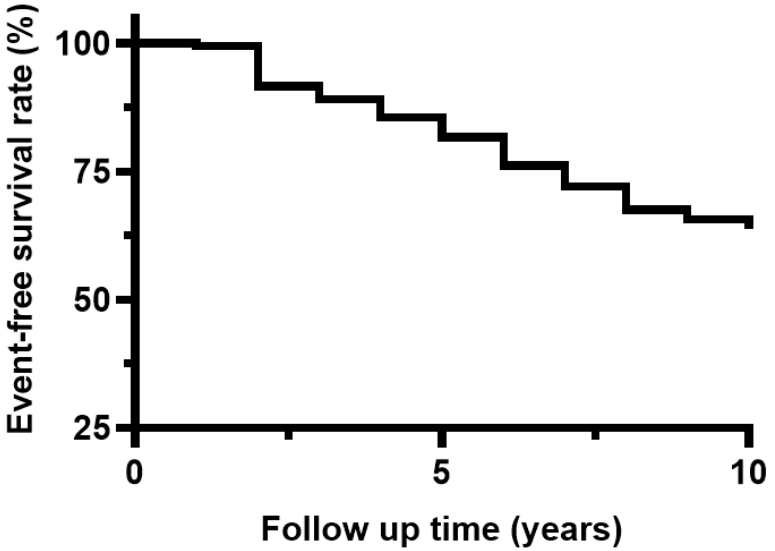
Variable		All (n=168)	Cluster A (n=61)	Cluster B (n=56)	Cluster C (n=51)	P value
Events	n (%)	65 (38.7)	16 (26.2)	28 (50.0)	21 (41.2)	0.028
Events occur rate per 100 patients-year	patients-year	3.87	3.28	5.56	2.94	
Thrombosis	n (%)	47 (28.0)	14 (23.0)	19 (33.9)	14 (27.5)	0.428
Arterial thrombosis	n (%)	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

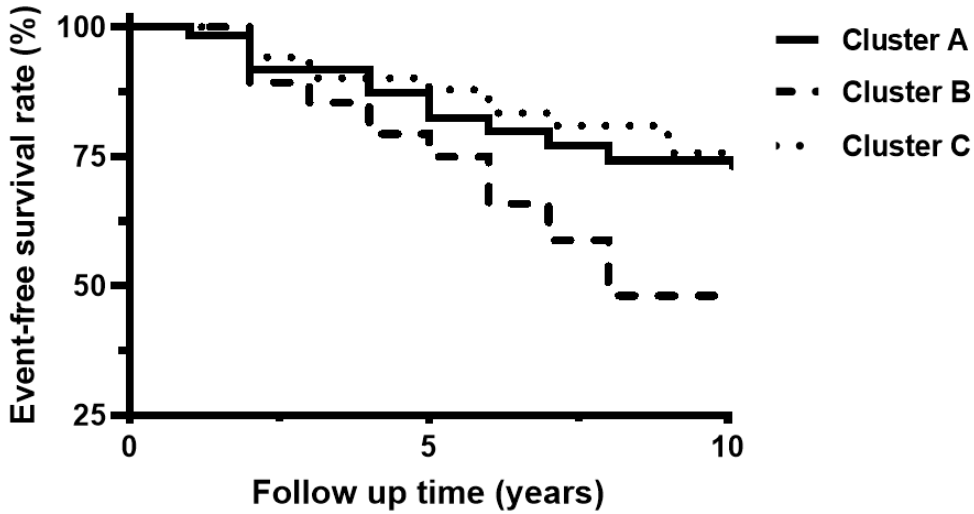
P-values <0.05. P-values were calculated using Kruskal-Wallis test or Fisher's Exact Test.

Figure 1A (all)



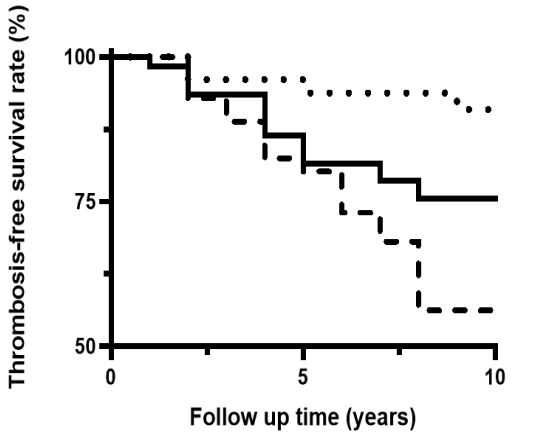
N	168(0)	140(14)	112(28)	81(40)	67(48)

Figure 1B (Cluster)



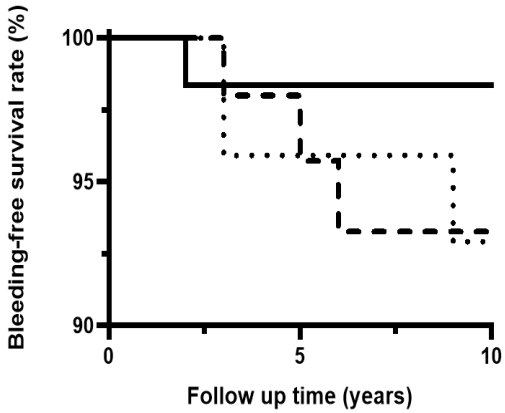
Cluster A	61(0)	47(5)	36(9)	27(10)	22(13)
Cluster B	56(0)	46(6)	36(13)	22(20)	16(24)
Cluster C	51(0)	47(2)	40(5)	32(8)	29(11)

Figure 2A
(Recurrent thrombosis)



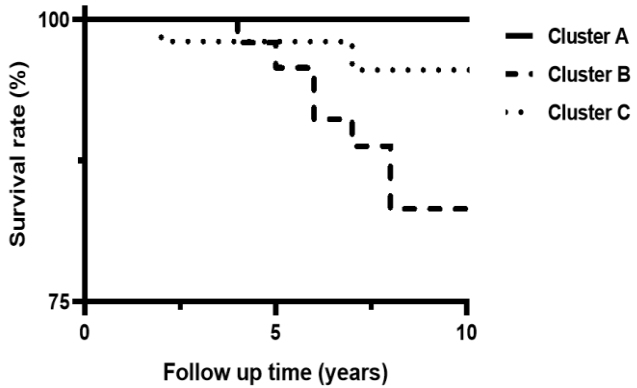
Cluster A	61(0)	47(4)	35(9)	26(10)	21(11)
Cluster B	56(0)	46(4)	36(10)	23(15)	17(19)
Cluster C	51(0)	47(2)	41(3)	34(3)	32(4)

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)