

SUPPORTING INFORMATION

TABLE S1

TABLE S2

TABLE S3

TABLE S4

TABLE S5

TABLE S6

FIGURE S1

FIGURE S2

TABLE S1 Baseline variables included in the cluster analyses

Variable	Total number of patients	Number of patients with available data	% of patients with available data
Antinuclear antibodies	253	186	73.5
IgG anti-cardiolipin, IU	253	215	85.0
IgM anti-cardiolipin, IU	253	212	83.8
Age, years	253	244	96.4
Transient ischemic attack	253	209	82.6
Stroke	253	209	82.6
IgG anti- β 2GP1, IU	253	214	84.6
IgM anti- β 2GP1, IU	253	212	83.8
Cancer	253	243	96.0
Catastrophic APS	253	248	98.0
Dyslipidemia	253	195	77.1
Pulmonary embolism	253	235	92.9
Arterial hypertension	253	198	78.3
Myocardial infarction	253	209	82.6
Libman Sachs endocarditis	253	250	98.8
Livedo reticularis	253	250	98.8
Thrombotic microangiopathy	253	250	98.8
Number of obstetrical adverse events	253	230	90.9
Neurological manifestations	253	250	98.8
Autoimmune cytopenia	253	251	99.2
APS nephropathy	253	250	98.8
Three or more unexplained consecutive spontaneous miscarriage before the 10th week	253	210	83.0

Preeclampsia, HELLP syndrome or placental abruption	253	211	83.4
Premature births before the 34th week	253	210	83.0
One or more unexplained deaths at or beyond the 10th week of gestation	253	208	82.2
Obstetrical phenotype	253	208	82.2
aPL carrier	253	253	100.0
Non-criteria manifestations	253	253	100.0
Thrombotic phenotype	253	253	100.0
Female sex	253	253	100.0
Arterial thrombosis	253	240	94.9
Triple positivity, n (%)	253	244	96.4
Deep vein thrombosis	253	239	94.5

Note: All data with more than 30% of missing data were excluded from the imputation.

Abbreviations: aPL, antiphospholipid; APS, antiphospholipid syndrome; β 2GP1, beta-2 glycoprotein 1; HELLP, Hemolysis, Elevated Liver enzymes, and Low Platelet count; Ig: immunoglobulin.

Table S2: Event-free cumulative incidence

Cluster	Patients numbers (n)	1 year		5 years		10 years	
		Event (n)	Event rate (%) [95% CI]	Event (n)	Event rate (%) [95% CI]	Event (n)	Event rate (%) [95% CI]
Total population	253	14	6.5% [3.1; 9.7]	34	19.1% [12.9 ; 24.8]	44	33.8% [23.0; 43.1]
Cluster 1	101	0	0.0% [0.0; 0.0]	0	0.0% [0.0; 0.0]	0	0.0% [0.0; 0.0]
Cluster 2	67	8	12.4% [4.0; 20.2]	12	20.1% [9.1; 29.8]	16	39.0% [16.3; 55.5]
Cluster 3	58	5	9.4% [1.2; 17.0]	13	27.6% [13.4; 39.5]	15	35.8% [17.5; 50.1]
Cluster 4	27	1	3.7% [0.0; 10.6]	9	35.2% [13.6; 51.4]	13	57.4% [29.1; 74.4]

Relapse-free log-rank test according to clusters:Global Log-rank test: $p = 0.0002$ Log rank test cluster 1 vs cluster 2: $p = 0.0002$ Log rank test cluster 1 vs cluster 3: $p = 0.0001$ Log rank test cluster 1 vs cluster 4: $p = 0.000004$ Log rank test cluster 2 vs cluster 3: $p = 0.9$ Log rank test cluster 2 vs cluster 4: $p = 0.2$ Log rank test cluster 3 vs cluster 4: $p = 0.2$

Table S3: Overall survival cumulative incidence

Cluster	Patients numbers (n)	1 year		5 years		10 years	
		Event (n)	Relapse rate (%) [95% CI]	Event (n)	Relapse rate (%) [95% CI]	Event (n)	Relapse rate (%) [95% CI]
Total population	253	3	1.4% [0.0 ; 3.1]	13	7.6% [3.4 ; 11.5]	16	11.4% [5.5 ; 17.0]
Cluster 1	101	1	1.5% [0.0 ; 4.2]	3	6.3% [0.0 ; 13.1]	3	6.3% [0.0 ; 13.1]
Cluster 2	67	1	1.6% [0.0 ; 4.7]	7	13.0% [3.4 ; 21.7]	9	19.6% [6.4 ; 30.9]
Cluster 3	58	1	1.9% [0.0 ; 5.6]	3	6.0% [0.0 ; 12.4]	3	6.0% [0.0 ; 12.4]
Cluster 4	27	0	0.0% [0.0 ; 0.0]	0	0.0% [0.0 ; 0.0]	1	6.3% [0.0 ; 17.4]

Overall survival log-rank test according to clusters:

Global Log-rank test: p= 0.2

Log rank test cluster 1 vs cluster 2: p= 0.3

Log rank test cluster 1 vs cluster 3: p= 1

Log rank test cluster 1 vs cluster 4: p= 0.4

Log rank test cluster 2 vs cluster 3: p= 0.1

Log rank test cluster 2 vs cluster 4: p= 0.1

Log rank test cluster 3 vs cluster 4: p= 0.7

Table S4: Individual characteristics of patient who presented an antiphospholipid event

Patient number	Sex	Age	Cardiovascular risk factors	aPL profile	Clinical phenotype at baseline	Cluster	Follow-up duration (months)	Event type	Type of antithrombotic treatment at event occurrence
10	Female	24	None	Triple positive	Thrombotic	4	60	VTE	VKA and antiagregant
11	Female	32	None	Triple positive	Thrombotic	4	0	VTE	VKA
19	Female	42	None	Double positive (a β ₂ GPI & LA)	Thrombotic	2	38	ATE	VKA
50	Male	61	None	Double positive (aCL & LA)	Thrombotic	2	24	VTE	VKA
65	Female	38	None	Triple positive	Thrombotic and obstetrical	3	41	ATE	VKA
111	Female	84	Arterial hypertension and dyslipidemia	Double positive (a β ₂ GPI & aCL)	Thrombotic	2	0	VTE	None
116	Male	66	Arterial hypertension and dyslipidemia	Double positive (a β ₂ GPI & aCL)	Thrombotic	2	10	ATE	Antiagregant
122	Male	64	None	Double positive (a β ₂ GPI & aCL)	Thrombotic	2	13	VTE	VKA
126	Male	73	Arterial hypertension and dyslipidemia	Triple positive	Thrombotic	4	12	ATE	VKA
142	Female	52	Arterial hypertension, dyslipidemia and diabetes mellitus	Simple positive (aCL)	Thrombotic	4	48	ATE	None
166	Female	65	Arterial hypertension, dyslipidemia and diabetes mellitus	Double positive (a β ₂ GPI & aCL)	Thrombotic	3	17	VTE	VKA
183	Female	46	None	Simple positive (aCL)	Thrombotic	4	108	VTE	None
188	Female	87	Arterial hypertension	Double positive (a β ₂ GPI & aCL)	Thrombotic	2	1	ATE	Antiagregant
189	Female	40	Arterial hypertension, dyslipidemia and active smoking	NA	Thrombotic and obstetrical	3	5	ATE	VKA
198	Female	33	Arterial hypertension	Triple positive	Thrombotic and obstetrical	4	24	OE	VKA

201	Female	66	Arterial hypertension and dyslipidemia	Triple positive	Thrombotic	2	5	VTE	None
204	Female	30	Active smoking	Triple positive	Thrombotic and obstetrical	4	29	OE	Antiagregant
213	Female	35	Arterial hypertension and active smoking	Triple positive	Thrombotic and obstetrical	4	27	ATE	Antiagregant
224	Female	49	Arterial hypertension and active smoking	Triple positive	Thrombotic	4	17	VTE	VKA
229	Female	40	None	Triple positive	Thrombotic and obstetrical	4	12	VTE	VKA
263	Female	30	None	Simple positive (acL)	Thrombotic	2	108	VTE	VKA
264	Male	35	None	Simple positive (LA)	Thrombotic	2	1	VTE	VKA
292	Female	80	Arterial hypertension and dyslipidemia	Double positive (aβ ₂ GPI & aCL)	Thrombotic	2	101	VTE	VKA
297	Male	78	Dyslipidemia	Double positive (aβ ₂ GPI & aCL)	Thrombotic	2	1	ATE	Antiagregant
305	Female	40	Diabetes mellitus	Double positive (aβ ₂ GPI & aCL)	Thrombotic and obstetrical	3	1	VTE	None VKA and antiagregant
310	Male	62	None	Triple positive	Thrombotic	4	45	ATE	None
314	Female	36	None	Triple positive	Obstetrical	3	39	OE	None
319	Female	37	None	NA	Obstetrical	3	40	OE	None
323	Male	52	None	Triple positive	Thrombotic	2	69	VTE	VKA
337	Male	43	None	Double positive (aβ ₂ GPI & aCL)	Thrombotic	2	46	VTE	VKA
343	Male	41	Active smoking and diabetes mellitus	Triple positive	Thrombotic	4	61	VTE	VKA and antiagregant
346	Female	82	None	Triple positive	Thrombotic	4	115	VTE	NA
348	Male	47	None	Simple positive (LA)	Thrombotic	2	64	VTE	VKA
356	Male	62	None	Simple positive (acL)	Thrombotic	2	9	ATE	VKA and antiagregant
361	Male	62	Arterial hypertension, dyslipidemia, active smoking and diabeetes mellitus	Double positive (aβ ₂ GPI & aCL)	Thrombotic	2	5	VTE	VKA
392	Female	36	None	D	Obstetrical	3	48	OE	None

406	Female	67	Arterial hypertension	Triple positive	Thrombotic and obstetrical	3	119	VTE	VKA
416	Female	65	Arterial hypertension	NA	Thrombotic and obstetrical	3	11	VTE	Antiagregant
422	Female	75	None	NA	Thrombotic and obstetrical	3	1	VTE	VKA and antiagregant
483	Female	51	None	Simple positive (LA)	Thrombotic and obstetrical	3	33	VTE	NA
486	Female	61	Arterial hypertension	Simple positive (LA)	Thrombotic and obstetrical	3	11	VTE	NA
487	Female	46	None	Simple positive (LA)	Thrombotic and obstetrical	3	32	ATE	Antiagregant
491	Female	28	None	Simple positive (LA)	Thrombotic and obstetrical	3	60	VTE	VKA
492	Female	48	None	Simple positive (LA)	Thrombotic and obstetrical	3	36	OE	NA

Abbreviations : a β ₂GPI : anti- β ₂ glycoprotein I antibody ; aCL : anticardiolipin antibody ; LA : lupus anticoagulant ; aPL : antiphospholipid antibodies ; VTE : venous thrombo-embolic event ; ATE arterial thrombo-embolic event ; OE : obstetrical event ; NA : non available

Table S5: Cause of death

Patient number	Age	aPL profile	Clinical phenotype at baseline	Event type	Cluster	Cause of death
52	55	Triple positive	Thrombotic	VTE	4	Acute heart failure
86	64	Simple positive (a β_2 GPI)	Thrombotic	None	2	Unkown
90	73	Triple positive	Thrombotic	None	2	Sepsis in diffuse large B-cell lymphomadiffuse large B-cell lymphoma
137	87	Double positive (a β_2 GPI & aCL)	Asymptomatic	None	1	Prostate cancer (adenocarcinoma)
142	52	Simple positive (aCL)	Thrombotic	ATE	4	Acute intestinal ischemia
158	44	Simple positive (aCL)	Thrombotic	None	2	Unkown
166	65	Double positive (a β_2 GPI & aCL)	Thrombotic	VTE	3	Unkown
178	62	Simple positive (aCL)	Asymptomatic	None	1	Thrombotic microangiopathy
188	87	Double positive (a β_2 GPI & aCL)	Thrombotic	ATE	2	Respiratory failure due to bacterial pneumomia
225	59	Simple positive (aCL)	Thrombotic	None	2	Unkown
236	69	Double positive (a β_2 GPI & aCL)	Thrombotic	None	2	Hepatic encephalopathy
247	83	Simple positive (aCL)	Thrombotic	None	3	Unkown
251	76	Simple positive (LA)	Asymptomatic	None	1	Autoimmune hemolytic anemia
286	79	Simple positive (aCL)	Thrombotic	None	2	Cardiac arrest
290	59	Simple positive (aCL)	Thrombotic	None	2	Septic shock due to P. aeruginosa pneumonia
292	80	Double positive (a β_2 GPI & aCL)	Thrombotic	VTE	2	Unkown
297	78	Simple positive (a β_2 GPI)	Thrombotic	ATE	2	SARS-CoV-2 pneumonia
310	62	Triple positive	Thrombotic	ATE	4	Unkown
356	62	Simple positive (aCL)	Thrombotic	ATE	2	Acute heart failure
361	62	Double positive (a β_2 GPI & aCL)	Thrombotic	VTE	2	Multiple organ dysfunction syndrome
445	83	Double positive (a β_2 GPI & aCL)	Asymptomatic	None	3	Unkown

Abbreviations : a β_2 GPI : anti- β_2 glycoprotein I antibody ; aCL : anticardiolipin antibody ; LA : lupus anticoagulant ; VTE : venous thrombo-embolic event ; ATE arterial thrombo-embolic event ; OE : obstetrical event ; NA : non available

TABLE S6 Patient characteristics, according to clusters with additional comparison between cluster 2, 3 and 4

	All patients N = 253	Cluster 1 N = 101	Cluster 2 N = 67	Cluster 3 N = 58	p*	p**	Cluster 4 N = 27	p***
Female sex, n (%)	174 (68.8)	63 (62.4)	31 (46.3)	58 (100.0)	<0.001	<0.01	22 (81.5)	<0.01
Age (years, median, IQR)	52.0 [38.0, 65.0]	54.0 [41.0, 62.0]	58.0 [43.5, 70.0]	48.0 [36.0, 62.0]	0.04	<0.01	41.0 [33.5, 54.5]	0.25
Arterial hypertension, n (%)	81 (40.9)	27 (35.1)	23 (46.0)	22 (44.0)	1.00	1.00	9 (42.9)	1.00
Dyslipidemia, n (%)	49 (25.1)	16 (1.3)	15 (30.6)	12 (24.0)	0.61	1.00	6 (28.6)	0.92
Tobacco, n (%)	35 (26.5)	15 (27.3)	10 (22.7)	3 (23.1)	1.00	0.47	7 (35.0)	0.73
Diabetes mellitus, n (%)	22 (15.5)	8 (13.3)	6 (13.0)	6 (40.0)	0.06	1.00	2 (9.5)	0.08
Overweight, n (%)	52 (31.5)	14 (22.2)	12 (28.6)	16 (39.0)	0.44	0.13	10 (52.6)	0.48
IgG anti-cardiolipin (IU, median, IQR)	13.0 [4.0, 43.0]	9.7 [3.0, 33.9]	8.6 [4.0, 50.0]	12.0 [5.0, 27.2]	0.75	0.001	51.5 [22.9, 200.3]	<0.001
IgG anti-cardiolipin medium-high titer positive, n (%)	64 (28.7)	19 (20.9)	21 (32.8)	10 (22.7)	0.36	0.05	14 (58.3)	<0.01
IgG anti-cardiolipin high titer positive, n (%)	30 (14.0)	7 (7.9)	9 (15.3)	6 (14.0)	1.00	0.12	8 (33.3)	0.12
IgM anti-cardiolipin (IU, median, IQR)	8.5 [2.0, 36.4]	7.0 [2.0, 30.2]	14.50 [2.6, 46.5]	7.0 [2.2, 20.0]	0.19	0.02	45.0 [7.5, 82.0]	<0.01
IgM anti-cardiolipin medium-high titer positive, n (%)	51 (24.1)	16 (18.0)	16 (27.6)	7 (16.7)	0.30	0.07	12 (52.2)	<0.01
IgM anti-cardiolipin high titer positive, n (%)	21 (9.9)	6 (6.7)	5 (8.6)	3 (7.1)	1.00	0.03	7 (30.4)	0.03
IgG anti-β2GP1 (IU, median, IQR)	3.4 [1.0, 25.0]	2.2 [1.0, 10.0]	3.0 [1.0, 19.2]	6.5 [1.0, 24.5]	0.73	<0.001	68.5 [11.4, 200.3]	<0.01
IgG anti-β2GP1 medium-high titer positive, n (%)	70 (31.4)	21 (23.6)	15 (24.6)	18 (39.1)	0.16	<0.01	16 (59.3)	0.16
IgG anti-β2GP1 high titer positive, n (%)	32 (15.0)	8 (9.0)	6 (10.2)	6 (14.3)	0.75	<0.001	12 (50.0)	<0.01
IgM anti-β2GP1 (IU, median, IQR)	3.00 [1.00, 24.00]	4.0 [1.0, 20.3]	2.5 [1.0, 28.7]	2.0 [1.0, 7.9]	0.18	<0.01	29.0 [2.0, 77.4]	<0.001
IgM anti-β2GP1 medium-high titer positive, n (%)	66 (29.7)	24 (27.0)	18 (29.5)	8 (17.4)	0.22	0.01	16 (61.5)	<0.001
IgM anti-β2GP1 high titer positive, n (%)	13 (6.1)	3 (3.4)	2 (3.4)	2 (4.8)	1.00	<0.01	6 (26.1)	0.04
LA, n (%)	102 (65.0)	38 (62.3)	19 (50.0)	26 (76.5)	0.04	0.04	19 (79.2)	1.00
Triple positivity, n (%)	47 (19.3)	10 (10.2)	7 (11.1)	7 (12.5)	1.00	<0.001	23 (85.2)	<0.001
Antinuclear antibodies, n (%)	58 (30.7)	15 (19.0)	5 (12.8)	18 (39.1)	0.01	<0.001	20 (80.0)	<0.01
Anti-dsDNA antibodies, n (%)	16 (12.4)	6 (10.3)	2 (6.9)	0 (0.0)	0.72	0.04	8 (32.0)	0.03

aPL carrier, n (%)	107 (42.3)	100 (99.0)	0 (0.0)	7 (12.1)	0.01	NA	0 (0.0)	0.14
Thrombotic phenotype, n (%)	125 (49.4)	1 (1.0)	67 (100.0)	31 (53.4)	<0.001	0.64	26 (96.3)	<0.001
Arterial thrombosis, n (%)	53 (22.1)	1 (1.0)	19 (28.4)	19 (38.8)	0.33	0.03	15 (55.6)	0.24
Stroke, n (%)	33 (15.8)	1 (1.1)	17 (27.9)	6 (15.4)	0.23	0.39	9 (40.9)	0.06
Transient ischemic attack, n (%)	3 (1.4)	0 (0.0)	1 (1.6)	1 (2.6)	1.00	1.00	1 (4.5)	1.00
Myocardial infarction, n (%)	12 (5.7)	0 (0.0)	4 (6.6)	4 (10.3)	0.77	0.25	4 (18.2)	0.63
Pulmonary embolism, n (%)	32 (13.6)	1 (1.0)	22 (34.4)	5 (10.0)	<0.01	0.15	4 (16.0)	0.71
Deep vein thrombosis, n (%)	60 (25.1)	0 (0.0)	33 (50.0)	14 (28.0)	0.03	1.00	13 (48.1)	0.13
Obstetrical phenotype, n (%)	56 (24.2)	0 (0.0)	0 (0.0)	47 (94.0)	<0.001	<0.001	9 (33.3)	<0.001
Number of obstetrical adverse events, n (%)					<0.001	<0.001		<0.001
	0	174 (75.7)	87 (100.0)	66 (100.0)			3 (6.0)	18 (66.7)
	1	33 (14.3)	0 (0.0)	0 (0.0)			29 (58.0)	4 (14.8)
	2	4 (1.7)	0 (0.0)	0 (0.0)			3 (6.0)	1 (3.7)
	≥3	19 (8.3)	0 (0.0)	0 (0.0)			15 (30.0)	4 (14.8)
One or more unexplained deaths at or beyond the 10th week of gestation, n (%)	11 (5.3)	0 (0.0)	0 (0.0)	8 (25.8)	<0.001	0.04	3 (11.1)	0.28
Three or more unexplained consecutive spontaneous miscarriage before the 10th week, n (%)	15 (7.1)	0 (0.0)	0 (0.0)	13 (39.4)	<0.001	0.16	2 (7.4)	0.01
Premature births before the 34th week, n (%)	7 (3.3)	0 (0.0)	0 (0.0)	5 (15.2)	<0.01	0.16	2 (7.4)	0.60
Preeclampsia, HELLP syndrome or placental abruption, n (%)	16 (7.6)	1 (1.2)	0 (0.0)	10 (29.4)	<0.001	<0.01	5 (18.5)	0.50
Non-criteria manifestations, n (%)	71 (28.2)	31 (30.7)	10 (15.2)	12 (20.7)	0.57	<0.001	18 (66.7)	<0.001
Autoimmune cytopenia, n (%)	26 (10.4)	13 (12.9)	0 (0.0)	4 (7.0)	0.09	<0.001	9 (33.3)	<0.01
Neurological manifestations, n (%)	22 (8.8)	9 (9.0)	5 (7.6)	4 (7.0)	1.00	0.49	4 (14.8)	0.46
APS nephropathy, n (%)	4 (1.6)	2 (2.0)	0 (0.0)	0 (0.0)	NA	0.15	2 (7.4)	0.19
Libman Sachs endocarditis, n (%)	3 (1.2)	0 (0.0)	0 (0.0)	1 (1.8)	0.94	0.15	2 (7.4)	0.50
Livedo reticularis, n (%)	7 (2.8)	4 (4.0)	0 (0.0)	3 (5.3)	0.19	NA	0 (0.0)	0.56
Thrombotic microangiopathy, n (%)	8 (3.2)	4 (4.0)	2 (3.0)	0 (0.0)	0.54	0.70	2 (7.4)	0.19

Catastrophic APS, n (%)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	NA	0.14	2 (7.4)	0.19
Anticoagulant treatment, n (%)	115 (48.5)	8 (8.2)	50 (80.6)	34 (64.2)	0.08	0.15	23 (95.8)	<0.01
Antiplatelet therapy, n (%)	80 (33.9)	15 (15.5)	26 (40.0)	27 (51.9)	0.27	0.35	12 (54.5)	1.00
Hydroxychloroquine, n (%)	32 (13.3)	8 (8.2)	4 (6.1)	10 (19.2)	0.06	<0.001	10 (40.0)	0.10
Steroids, n (%)	33 (14.2)	14 (14.7)	4 (6.1)	7 (14.3)	0.25	<0.01	8 (34.8)	0.09
Death, n (%)	21 (8.3)	3 (3.0)	12 (17.9)	3 (5.2)	0.06	0.62	3 (11.1)	0.59
Relapse, n (%)	44 (17.4)	0 (0.0)	16 (23.9)	15 (25.9)	0.96	0.04	13 (48.1)	0.07
Follow-up duration (months, median, IQR)	38.4 [11.5, 106.3]	120.0 [120.0, 120.0]	24.0 [5.0, 84.8]	36.0 [11.4, 48.0]	0.74	0.17	48.0 [24.0, 115.0]	0.24

Abbreviations: aPL, antiphospholipid; APS, antiphospholipid syndrome; β 2GP1, beta-2 glycoprotein 1; dsDNA, double-stranded deoxyribonucleic acid; HELLP, Hemolysis, Elevated Liver enzymes, and Low Platelet count; Ig: immunoglobulin; IQR, interquartile range; LA, lupus anticoagulant.

* Comparison between cluster 2 and cluster 3

** Comparison between cluster 2 and cluster 4

*** Comparison between cluster 3 and cluster 4

Qualitative variables and quantitative variables were compared between clusters using Fisher and Kruskal-Wallis tests, respectively.

Figure S1 Determination of optimal clusters number, using three different methods. A. Gap statistic method (Tibshirani R, Walther G, Hastie T. Estimating the number of clusters in a data set via the gap statistic. *J R Stat Soc Ser B Stat Methodol.* 2001;63(2);411-423). B. Elbow method. C. Silhouette method (Rousseeuw P. Silhouettes: a graphical aid to the interpretation and validation of cluster analysis. *J Comput Appl Math.* 1987;20:53-65). All methods suggested four clusters.

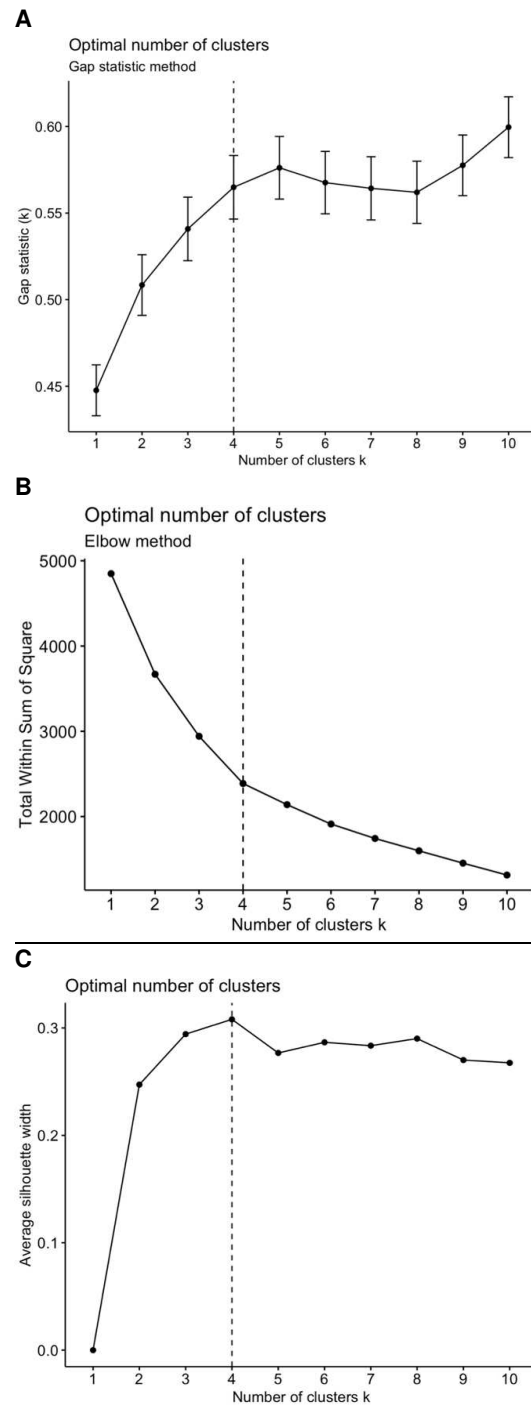


Figure S2 – Overall survival cumulative incidence curves, according to clusters.

