**Supplementary material**

**Supplementary table 1.** Characteristics of SSc patients included in this study who had a thrombotic event.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Patient****and sex** | **SSc subtype** | **Thrombotic event** | **Disease duration at the time of the event (years)** | **LA** | **aCL (UGPL/mL)** | **Anti -β2GP1 (UA/mL)** | **Time between event and aPL testing (years)** | **Age at the event (years)** | **APS criteria** |
| 6 | F | lcSSc | PE | +9 | neg | 0 | 0 | 3 | 71 |  |
| 8 | F | lcSSc | ALI | 0 | neg | 0 | 0 | 4 | 52 |  |
| **9** | **F** | **lcSSc** | **PE** | **+7** | **pos** | **5** | **56** | **9** | **50** | **Yes** |
| 18 | F | lcSSc | DVT1DVT2 | - 37- 33 | neg | 3 | 4 | 4036 | 2226 |  |
| 38 | M | lcSSc | Stroke/TIA | + 8 | neg | 0 | 0 | 1 | 68 |  |
| 48 | F | lcSSc | DVT | 0 | neg | 0 | 0 | 27 | 53 |  |
| 52 | F | lcSSc | DVTMI | - 5+ 8 | neg | 4 | 4 | 273 | 6275 |  |
| 60 | M | lcSSc | BTUA | 0 | neg | 0 | 5 | 1 | 59 |  |
| 62 | F | lcSSc | PEBTUA | +10 | neg | 0 | 0 | 23 | 4140 |  |
| 65 | M | lcSSc | ALI | NA | neg | 4 | 7 | NA | NA |  |
| 72 | F | lcSSc | DVT | NA | neg | 0 | 0 | NA | NA |  |
| 85 | F | lcSSc | 3 DVT | NA | neg | 4 | 3 | NA | NA |  |
| 89 | M | lcSSc | 3 DVT | NA | neg | 3 | 0 | NA | NA |  |
| 96 | F | lcSSc | DVT | NA | neg | 0 | 0 | NA | NA |  |
| **97** | **F** | **lcSSc** | **DVT1****DVT2****DVT 3****Stroke/TIA** | **+ 5** **+ 6** **+ 7****- 3** | **neg** | **5** | **47** | **2** **1** **0****10** | **65** **66** **67****57** |  |
| **101** | **F** | **lcSSc** | **DVT** | **0** | **pos** | **0** | **4** | **17** | **54** | **Yes** |
| 105 | F | dcSSc | MI, Stroke/TIA | + 7 | na | 0 | 0 | 1 | 73 |  |
| 107 | F | lcSSc | DVT | - 12 | neg | 3 | 3 | 41 | 28 |  |
| **112** | **F** | lcSSc | **DVT1****4 DVT, 1 PE****MI** | **+ 18****NA****+ 19** | **neg** | **4** | **15** | **3****NA****2** | **65****NA****66** |  |
| 121 | F | lcSSc | DVT | + 20 | neg | 4 | 6 | 11 | 35 |  |
| 123 | F | lcSSc | DVT 1DVT 2 | + 14+ 28 | neg | 5 | 4 | 151 | 5872 |  |
| 126 | **F** | lcSSc | **Stroke/TIA** | **- 3** | **neg** | **19** | **17** | **8** | **50** |  |
| 130 | F | lcSSc | Stroke/TIA 1Stroke/TIA 2 | + 7+ 10 | neg | 3 | 0 | 107 | 3437 |  |
| 131 | F | dcSSc | DVT | + 15 | neg | 0 | 0 | 5 | 67 |  |
| 143 | F | lcSSc | DVT | + 3 | neg | 0 | 0 | 4 | 67 |  |
| **145** | **F** | lcSSc | **DVT 1****DVT 2** | **- 24****+ 3** | **neg** | **4** | **12** | **30****3** | **26****53** |  |
| 148 | F | lcSSc | Stroke/TIA | - 17 | neg | 5 | 0 | 32 | 36 |  |
| 151 | F | lcSSc | Stroke/TIA | + 15 | neg | 0 | 7 | 8 | 74 |  |
| 156 | F | lcSSc | DVTStroke/TIA | + 1NA | neg | 0 | 0 | 0NA | 65NA |  |
| 157 | F | lcSSc | BTUA | + 16 | neg | 3 | 3 | 1 | 68 |  |
| 164 | F | lcSSc | Stroke/TIA | + 8 | neg | 0 | 0 | 1 | 72 |  |
| 170 | F | lcSSc | MI | + 29 | neg | 3 | 4 | 6 | 76 |  |
| 173 | M | lcSSc | BTUA | NA | neg | 3 | 0 | NA | NA |  |
| 176 | F | lcSSc | DVT | + 1 | neg | 3 | 5 | 3 | 31 |  |
| 188 | F | lcSSc | MI | - 19 | neg | 0 | 0 | 25 | 56 |  |
| 191 | F | lcSSc | PE | NA | neg | 0 | 0 | NA | NA |  |
| 192 | M | lcSSc | DVTALI | NA0 | neg | 3 | 3 | NA18 | NA39 |  |
| 196 | F | lcSSc | Stroke/TIA | + 16 | neg | 3 | 0 | 1 | 74 |  |
| 197 | F | lcSSc | DVT | - 40 | neg | 0 | 0 | 40 | 37 |  |
| 204 | F | lcSSc | PE | + 1 | neg | 8 | 6 | 18 | 61 |  |
| 207 | F | lcSSc | DVT1, PE 1DVT2, PE 2 | - 10+ 13 | neg | 5 | 0 | 252 | 3457 |  |
| 215 | F | lcSSc | DVT 1DVT2DVT 3 | - 29- 24- 4 | neg | 0 | 7 | 34299 | 354060 |  |
| 222 | F | lcSSc | Stroke/TIA | + 29 | neg | 0 | 0 | 1 | 59 |  |
| 227 | F | lcSSc | PE | + 6 | neg | 3 | 0 | 12 | 56 |  |
| 231 | F | dcSSc | PE | + 16 | neg | 3 | 0 | 1 | 39 |  |

lcSSc = limited cutaneous SSc ; dcSSc = diffuse cutaneous SSc ; PE = pulmonary embolism ; DVT = deep venous thrombosis ; MI = myocardial infarction; BTUA = bilateral thrombosis of ulnar arteries; Stroke/TIA = stroke or transient ischemic attack; ALI = acute limb ischemia; pos = positive; neg = negative. APS: antiphospholipid syndrome

Supplementary table 2. Patients’ characteristics according to thrombotic or obstetric history.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Arterial thrombosis | Venous thrombosis | Miscarriage |
| no | yes | no | yes | no | yes |
| Sex, no. (%) female | 185 (82) | 18 (82) | 178 (81) | 27 (93) | na | na |
| Age, mean (SD) years | **59 (13)\*\*** | **67 (11)\*\*** | **59 (13)\*** | **64 (11)\*** | 59 (15) | 57 (11) |
| Age at onset of disease, mean (SD) years | 47 (14) | 52 (12) | 47 (14) | 50 (15) | 46 (14) | 46,5 (12) |
| Disease duration, mean (SD) years | 10,4 (8,9) | 12,7 (8,7) | 10,4 (9) | 13,3 (8) | 11,6 (9,2) | 9,8 (7,4) |
| Disease subtypeLimited Diffuse | 180 (80)ᶿ45 (20) | 21 (95)ᶿ1 (5)  | 176 (80)43 (20) | 27 (93)2 (7) | 129 (88)ᶿ18 (12)ᶿ | 30 (75)ᶿ10 (25)ᶿ |
| Pulmonary arterial hypertension, no. (%) | 15 (7) | 0  | 11 (5)ᶿ | 4 (14)ᶿ | 8 (6)  | 2 (6) |
| Interstitial lung disease, no. | 93 (45) | 11 (50) | 92 (46) | 11 (41) | 53 (40) | 17 (46) |
| Digital ulceration, no. (%) | 72 (34) | 6 (30) | 71 (34) | 8 (31) | 44 (31) | 15 (38) |
| Renal crisis, no. (%) | 0ᶿ | 1 (5)ᶿ | 1 (1) | 0 | 1 (1) | 0 |
| BMI | 25 (5,7) | 26 (6,3) | 24,9 (5,6) | 26.5 (5,7) | 25,3 (5,3) | 25,2 (7,3) |
| Tobacco | 88 (39) | 9 (41) | 90 (41) | 8 (29) | 52 (35) | 15 (37) |
| ANA specificity, no. (%)ACAAnti–topo IAnti-RNA pol IIIAnti–U1RNP | 124 (58)45 (21)7 (3)8 (4) | 13 (59)5 (23)0 1 (5) | **117 (56)\***44 (21)7 (3)8 (4) | **22 (79)\***5 (18)0 1 (4) | 92 (66)29 (21)4 (3)7 (5) | 25 (64)4 (10)1 (3)2 (5) |
| CRP (> 10 mg/L) | 19 (8) | 2 (9) | 17 (8) | 4 (14) | 12 (8) | 4 (10) |
| Hypergammaglobulinemia | 29 (13) | 1 (5) | 28 (13) | 2 (7) | 13 (9) | 7 (17) |
| HbA1c (> 6.5%) | 5 (2) | 1 (5) | 3 (1) | 2 (7) | 3 (2) | 1 (3) |
| Rheumatoid factor |  |  |  |  |  |  |
| APLIgG ACLIgG anti-B2GpILA | 13 (6)2 (1)8 (4) ᶿ4 (2) | 3 (14)1 (5)3 (14) ᶿ0  | **11 (5)\***3 (1)**7 (3)\***2 (1)ᶿ | **5 (17)\***0**4 (14)\***2 (7)ᶿ | 7 (5)2 (1)4 (3)ᶿ2 (1) | 5 (12)04 (10)ᶿ2 (5) |

ᶿ p < 0.10, \* p < 0.05, \*\* p < 0.01, \*\*\* p < 0.001

|  |  |  |
| --- | --- | --- |
|  | PAH | UD |
| no | yes | no | yes |
| Sex, no. (%) female | 181 (83) | 13 (87) | 131 (83) | 65 (82) |
| Age, mean (SD) years | 59 (13) | 65 (10) | 61 (12)ᶿ | 57 (14)ᶿ |
| Age at onset of disease, mean (SD) years | 48 (14) | 49 (12) | 49 (13)ᶿ | 44 (15) ᶿ |
| Disease duration, mean (SD) years | 10,7 (9) | 13,8 (9,1) | 10,3 (9) | 12,3 (8,9) |
| Disease subtypeLimited Diffuse | 184 (84)34 (16) | 10 (67)5 (33) | **157 (89)\*****18 (11)\*** | **55 (70)\*****24 (30)\*** |
| Pulmonary arterial hypertension, no. (%) | Na | na | 8 (5) | 7 (9) |
| Interstitial lung disease, no. | 87 (43) | 10 (67) | **53 (37)\*\*** | **40 (56)\*\*** |
| Digital ulceration, no. (%) | 68 (33) | 7 (47) | na | na |
| Renal crisis, no. (%) | 1 (1) | 0 | 1 (1) | 0 |
| BMI | 25 (5,6) | 24,9 (7,6) | **25,7 (5,8)\*** | **23,7 (5)\*** |
| Tobacco | **91 (42)\*** | **2 (13)\*** | 62 (39) | 33 (42) |
| ANA specificity, no. (%)ACAAnti–topo IAnti-RNA pol IIIAnti–U1RNP | 124 (60)41 (20)6 (3)7 (3) | 7 (47)5 (33)01 (7) | **98 (65)\*****22 (15)\***4 (3)8 (5) | **37 (49)\*****22 (29)\***3 (4)1 (1) |
| CRP (> 10 mg/L) | 20 (9) | 1 (7) | 15 (10) | 5 (6) |
| Hypergammaglobulinemia | 25 (11) | 3 (20) | 15 (10)ᶿ | 14 (18)ᶿ |
| HbA1c (> 6.5%) | 6 (3) | 0 | 5 (3,52) | 1 (1,4) |
| Rheumatoid factor |  |  |  |  |
| APLIgG ACLIgG anti-B2GpILA | 15 (7)3 (1)10 (5)4 (2) | 1 (7)01 (7)0 | 12 (8)1 (1)**9 (6)\***4 (3) | 2 (3)2 (3)**0\***0 |

Supplemental figure 1. Distribution of aCL and anti-B2GpI levels in the study population



Supplementary table 3. Correlation between aCL titers and clinical manifestations

|  |  |  |
| --- | --- | --- |
|  | aCL titers (UGPL/mL) |  |
|  | [0,1[ n=137 | [1,5[ n=91 | [5,20]n=21 | p |
| Sex, n (%) female | 114 (83) | 73 (80) | 18 (86) | 0.818 |
| Age, mean ± SD years | 58.6 (13.1) | 60.6 (13) | 60.5 (14.9) | 0.504 |
| Age at onset of disease, mean ± SD years | 48.4 (13.4) | 47.55 (13.9) | 42.69 (14.8) | 0.320 |
| Disease duration, mean ± SD years | 9.19 (7.8) | 12.11 (9.6) | 14.71 (11.2) | 0.016 |
| BMI mean ± SD | 24.5 (5.2) | 25.7 (6.3) | 26.6 (5.6) | 0.132 |
| Tobacco use, n (%) | 57 (42) | 36 (40) | 6 (29) | 0.545 |
| Systemic hypertension, n (%) | 64 (47) | 49 (54) | 12 (57) | 0.443 |
| Diabetes, n (%) | 5 (4) | 7 (8) | 0 | 0.258 |
| Dyslipidemia, n (%) | 61 (45) | 39 (43) | 12 (57) | 0.495 |
| Disease subtype, n (%)Limited Diffuse | 113 (82)24 (18) | 73 (80)18 (20) | 17 (81)4 (19) | 0.8800.880 |
| Pulmonary arterial hypertension, n (%) | 3 (2) | 9 (11) | 3 (16) | 0.007 |
| Interstitial lung disease, n (%) | 61 (49) | 34 (40) | 9 (43) | 0.406 |
| Digital ulceration, n (%) | 46 (35) | 23 (26) | 10 (53) | 0.079 |
| Renal crisis, n (%) | 1 (1) | 0 (0) | 0 (0) | 1 |
| Arterial or venous thrombosis, n (%) | 21 (16) | 17 (19) | 7 (33) | 0.142 |
| Arterial thrombosis, n (%)StrokeIschemiaMyocardial infarction | 11 (8)6 (4)1 (1)2 (1) | 8 (9)2(2)2(2)3(3) | 3 (14)3(14)0 (0)0 (0) | 0.5830.0640.6680.613 |
| Venous thrombosis, n (%)DVTPE | 12 (9)9 (7)3 (2) | 12 (13)10 (11)3 (3) | 5 (24)3(14)3 (14) | 0.0950.2800.044 |
| Miscarriage, n (%) | 21 (20) | 17 (26) | 2 (13) | 0.521 |
| ANA specificity, n (%)ACAAnti–topo IAnti-RNA pol IIIAnti–U1RNP | 55 (42)27 (21)5 (4)1 (1) | 36 (41)17 (20)2 (2)7 (8) | 8 (38)6 (29)0 (0)1 (5) | 0.960.6190.8470.014 |
| CRP>10 mg/L, n (%) | 11 (8) | 7 (8) | 3 (14) | 0.567 |
| Hypergammaglobulinemia, n (%) | 11 (8) | 17 (19) | 2 (10) | 0.050 |
| HbA1c>6.5%, n (%) | 2 (1) | 4 (4) | 0(0) | 0.341 |

Supplementary table 4. Correlation between anti-β2GpI titers and clinical manifestations

|  |  |
| --- | --- |
|  | **anti-β2GpI titers (UA/mL)** |
|  | [0,1[n=120 | [1,5[n=83 | [5,10[n=35 | [10,100]n=11 | p |
| Sex, n (%) female | 100 (83) | 65 (78) | 30 (86) | 10 (91) | 0.683 |
| Age, mean ± SD years | 59.6 (12.7) | 59 (14.5) | 58.8 (13.5) | 65.4 (7.1) | 0.495 |
| Age at onset of disease, mean ± SD years | 47.6 (12.9) | 47.5 (14.7) | 48.1 (15.3) | 48 (8.7) | 0.997 |
| Disease duration, mean ± SD years | 10.9 (9.5) | 10.2 (8) | 10.5 (9) | 13.6 (9.9) | 0.808 |
| BMI mean ± SD | 24.8 (5.6) | 25.1 (5.4) | 25.0 (6.0) | 29.6 (7.2) | 0.059 |
| Tobacco use, n (%) | 50 (42) | 37 (45) | 12 (34) | 0 (0) | 0.019 |
| Systemic hypertension, n (%) | 61 (51) | 41 (49) | 15 (43) | 8 (73) | 0.402 |
| Diabetes, n (%) | 6 (5) | 5 (6) | 1 (3) | 0 | 0.914 |
| Dyslipidemia, n (%) | 59 (49) | 27 (33) | 18 (51) | 8 (73) | 0.017 |
| Disease subtype, n (%)Limited Diffuse | 97 (81)23 (19) | 62 (75)21 (25) | 33 (94)2 (6) | 11 (100)0(0) | 0.0270.027 |
| Pulmonary arterial hypertension, n (%) | 7 (6) | 7 (9) | 0(0) | 1 (9) | 0.243 |
| Interstitial lung disease, n (%) | 57 (52) | 32 (42) | 12 (36) | 3 (27) | 0.198 |
| Digital ulceration, n (%) | 43 (38) | 23 (29) | 13 (38) | 0 (0) | 0.074 |
| Renal crisis, n (%) | 1 (1) | 0 (0) | 0 (0) | 0 (0) | 1 |
| Arterial or venous thrombosis, n (%) | 24 (20) | 9 (11) | 7(21) | 5 (45) | 0.038 |
| Arterial thrombosis, n (%)StrokeIschemiaMyocardial infarction | 12 (10)8 (7)1 (1)2 (2) | 4 (5)0 (0)1 (1)2 (3) | 3 (9)1 (3)1 (3)0 (0) | 3 (27)2 (18)0 (0)1 (9) | 0.0990.0090.6030.348 |
| Venous thrombosis, n (%)DVT PE | 14 (12)9 (8)6 (5) | 7 (9)7 (8)0 (0) | 4 (11)3 (9)1 (3) | 4 (36)3 (27)2 (18) | 0.0960.1950.016 |
| Miscarriage, n (%) | 19 (21) | 13 (22) | 4 (15) | 4 (50) | 0.237 |
| ANA specificity, n (%)ACAAnti–topo IAnti-RNA pol IIIAnti–U1RNP | 61 (54)19 (17)5 (4)4 (4) | 45 (56)24 (30)2(3)5 (6) | 23 (68)6 (18)0 (0)0 (0) | 10 (91)1 (9)0 (0)0 (0) | 0.0650.1170.7610.526 |
| CRP>10 mg/L, n (%) | 10 (8) | 9 (11) | 1 (3) | 1 (9) | 0.534 |
| Hypergammaglobulinemia, n (%) | 13 (11) | 12 (14) | 5 (14) | 0 (0) | 0.593 |
| HbA1c>6.5%, n (%) | 2 (2) | 4 (5) | 0 (0) | 0 (0) | 0.43 |

**Supplementary table 5.** Characteristics of the population included in the study, and comparison between aPL positive (persistent) vs. negative/non-persistent aPL patients (repeat testing).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | N (N aPL+) | Whole population(n=249) | Persistent aPL(n=7) | aPL negative or non-persistent aPL(n=206) | p |
| Sex, n (%) female | 249 (7) | 205 (82) | 7 (100) | 165 (80) | 0.351 |
| Age, mean ± SD years | 249 (7) | 59.5 ± 13.3 | 64.9 ± 6.4 | 59.0 ± 13.0 | 0.233 |
| Age at onset of disease, mean ± SD years | 204 (6) | 47.7 ± 13.7 | 52.1 ± 6.6 | 47.2 ± 13.6 | 0.381 |
| Disease duration, mean ± SD years | 204 (6) | 10.7 ± 8.9 | 11.6 ± 7.6 | 10.8 ± 8.9 | 0.843 |
| BMI mean ± SD | 232 (7) | 25.1 ± 5.7 | 33.3 ± 8.6 | 24.9 ± 5.4 | **<0.001** |
| Tobacco use, n (%) | 248 (7) | 99 (40) | 1 (14) | 87 (42) | 0.243 |
| Systemic hypertension, n (%) | 249 (7) | 125 (50) | 6 (86) | 99 (48) | 0.063 |
| Diabetes, n (%) | 249 (7) | 12 (5) | 1 (14) | 11 (5) | 0.338 |
| Dyslipidemia, n (%) | 249 (7) | 112 (45) | 5 (71) | 93 (45) | 0.252 |
| Disease subtype n (%)Limited Diffuse | 249 (7) | 203 (82)46 (18) | 7 (100)0 | 164 (80)42 (20) | 0.350 |
| Pulmonary arterial hypertension, n (%) | 233 (7) | 15 (6) | 1 (14) | 13 (7) | 0.402 |
| Interstitial lung disease, n (%) | 230 (7) | 104 (45) | 2 (29) | 93 (49) | 0.447 |
| Digital ulceration, n (%) | 236 (6) | 79 (33) | 0 | 71 (36) | 0.092 |
| Renal crisis, n (%) | 231 (7) | 1 (0) | 0 | 1 (1) | 1.000 |
| Arterial or venous thrombosis, n (%) | 246 (7) | 45 (18) | 4 (57) | 33 (16) | 0.019 |
| Arterial thrombosis, n (%) Stroke/transient ischemic attack Acute limb ischemia Myocardial infarction | 247 (7) | 22 (9)11 (4)3 (1)5 (2) | 1 (14)001 (14) | 14 (7)6 (3)3 (1)2 (1) | 0.4061.0001.0000.096 |
| Venous thrombosis, n (%) DVT PE | 248 (7) | 29 (12)22 (9)9 (4) | 4 (57)3 (43)2 (29) | 23 (11)17 (8)7 (3) | **0.006****0.020****0.030** |
| Miscarriage, n (%) | 187 (6) | 40 (21) | 4 (67) | 32 (21) | **0.023** |
| ANA specificity, n (%)ACAAnti–topo IAnti-RNA pol IIIAnti–U1RNP | 238 (7) | 139 (58)50 (21)7 (3)9 (4) | 6 (86)1 (14)00 | 109 (55)45 (23)4 (2)7 (4) | 0.1401.0001.0001.000 |
| CRP > 10 mg/L, n (%) | 248 (7) | 21 (8) | 0 | 19 (9) | 1.000 |
| Hypergammaglobulinemia, n (%) | 249 (7) | 30 (12) | 0 | 29 (14) | 0.597 |
| HbA1c > 6.5%, n (%) | 247 (7) | 6 (2) | 0 | 6 (3) | 1.000 |

**Supplementary table 6.** Prevalence of persistent aPL in this study and frequencies of LA, aCL and anti-β2GpI in SSc patients with persistent aPL (n=213, repeat testing).

|  |  |  |
| --- | --- | --- |
|  | Prevalence of persistent aPL in this study (% and 95% CI) | Frequencies of LA, aCL and anti-β2GpI in SSc patients with persistent aPL (%) |
|  ≥ 1 aPL | 3.3 (1.5-6.9) | --- |
| LA | 0.9 (0.1-3.4) | 2 |
| aCL | 0 | 0 |
| Anti-β2GpI | 2.4 (0.9-5.7) | 5 |

**Supplementary table 7.** Univariate and multivariate comparisons of associations between persistent aPL in SSc patients and clinical manifestations.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Univariate OR (95% CI)** | **p** | **Multivariate OR (95% CI) \*** | **p** |
| Arterial or venous thrombosis | **6.81 (1.10-48.62)** | **0.019** | **6.65 (1.17-45.10)** | **0.036** |
| Arterial thrombosis | 2.26 (0.05-20.81) | 0.406 | 2.61 (0.12-24.60) | 0.442 |
| Venous thrombosis | **10.33 (1.64-75.04)** | **0.006** | **7.93 (1.38-53.40)** | **0.022** |
| Miscarriage | **7.56 (1.03-87.20)** | **0.023** | **18.35 (2.83-163.34)** | **0.003** |
| Pulmonary arterial hypertension | 2.31 (0.05-21.42) | 0.402 | 1.31 (0.06-10.95) | 0.821 |

\* OR adjusted for sex, age at aPL testing, skin involvement, tobacco use, systemic hypertension, ACA positivity

**Supplementary table 8:** Characteristics of the studies included in the meta-analysis and results of methodological quality assessment using the QUADAS-2 tool.

Items of modified QUADAS-2 tool used in this study:

1. Was a consecutive or random sample of patients enrolled?
2. Did the study avoid inappropriate exclusions?
3. Was the method of aPL determination described?
4. Were all patients included in the study tested for aPL?

According to the QUADAS-2 manual, each item was assessed “yes”, “no” or “unclear”:

|  |  |
| --- | --- |
|  | Yes |
|  | No |
|  | Unclear |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Author, year (ref.) | Country*Ethnic origin of the patients* | Study design(time interval) | Length of follow-up or duration of disease | Method of aPLdetermination – Cut-off for ELISA | No. of SSc patients positive/tested for aPL | QUADAS |
| 1 | 2 | 3 | 4 |
| Antonioli *et al*, 2003 | Italy*NA* | Cohort (NA) | Mean duration = 13 years (range 1-42) | ELISA (homemade), >99th percentile | 8/60 (aCL-IgG/IgM)14/60 (anti-β2GP1-IgG/IgM) |  |  |  |  |
| Assous *et al*, 2005 | France*NA* | Cohort of consecutive patients (2001-2003) | 10 ± 2 yr\* | Immunoassays (homemade),>98th percentile (15 for aCL and 6 for anti-β2GP1) | 0/108 (LA)15/108 (aCL-IgG/IgM)5/108 (anti-β2GP1-IgG/IgM) |  |  |  |  |
| Buchanan *et al*, 1989 | Australia*Caucasian 100%* | NA | NA | ELISA (homemade), mean ± 3 SD of controls (20UI) | 3/35 (aCL-NA) |  |  |  |  |
| Enzenauer *et al*, 2006 | USA*NA* | NA | NA | ELISA (Biopostar reads), mean ± 2 SD of controls (22.6UI) | 10/82 (aCL-IgG) |  |  |  |  |
| Gupta *et al*, 2009 | India*NA* | Cross-sectionnal study (2002-2006) | Mean duration = 3 years | ELISA (Genesis Diagnostics), 12UI/mL | 2/72 (LA)6/72 (aCL-IgG/IgM) |  |  |  |  |
| Herrick *et al*, 1994 | UK*NA* | 60 unselected patients + 8 with sever ischaemia (NA) | Median duration = 12 years (Raynaud’s onset) | ELISA, 5UI | 13/68 (aCL-IgG) |  |  |  |  |
| Ihn *et al*, 1996 | Japan*NA* | NA | Mean duration = 7 years | ELISA (homemade), mean ± 3 SD of controls | 20/80 (aCL-IgG)8/80 (anti-β2GP1-IgG) |  |  |  |  |
| Liberati *et al*, 2010 | Brazil*NA* | Transversal study (NA) | 12.3 ± 8.9 yr\* | ELISA (Euroimmun), 15 UI/mL | 5/54 (aCL-IgG) |  |  |  |  |
| Lima *et al*, 1991 | Spain*NA* | NA | 10.1 ± 7.7 yr\* | ELISA, ≥ 5 UI | 0/35 (aCL-IgG/IgM) |  |  |  |  |
| Manoussakis *et al*, 1987 | Greece*NA* | Unselected (NA) | 7.0 ± 4.5 yr\* | ELISA (homemade), ≥ mean ± 4 SD of controls (2.3 UI) | 2/40 (aCL-IgG/IgM) |  |  |  |  |
| Marie *et al*, 2008 | France*NA* | Consecutive patients (NA) | Median duration = 5 years (range 1-40) | LA: dilute thromboplastine timeELISA (INOVA and Hemagen diagnostics), NA | 13/69 (aPL)3/69 (LA)13/69 (aCL-IgG/IgM)3/69 (anti-β2GP1-IgG/IgM) |  |  |  |  |
| Mellal *et al*, 2014 | Algeria*NA* | NA | 12.2 ± 9.3 yr\* | ELISA (INOVA) | 5/147 (aCL-IgG) |  |  |  |  |
| Merkel *et al*, 1996 | USA*NS* | Inception cohort of newly diagnosed CTD (1982-1987) | NS | ELISA (homemade), ≥ mean ± 5 SD of controls (10 UI) | 1/45 (aCL-IgG) |  |  |  |  |
| Mok *et al*, 2011 | China*Asian 100%* | Consecutive patients | Median duration = 9 (IQR 5.5-19.5) | LA (cf. Article)ELISA (homemade), 15 UI | 7/46 (LA+aCL-IgG) |  |  |  |  |
| Morrisroe *et al*, 2014 | Australia*NA* | Patients from a prospective cohort | 15.3 ± 13.9 yr\* | LA (cf. Article)ELISA (Vital diagnostics for aCL and Orgentec for anti-β2GP1), > 0 UI | 226/940 (LA+aCL-IgG/IgM+ anti-β2GP1-NA)0/940 (LA)98/940 (aCL-IgG)63/940 (anti-β2GP1-NA) |  |  |  |  |
| Parodi *et al*, 2001 | Italy*NA* | NA | NA | ELISA (Bouty/Orgentec) | 11/90 (aCL-IgG+anti-β2GP1-IgG)11/90 (aCL-IgG)3/90 (anti-β2GP1-IgG) |  |  |  |  |
| Picillo *et al*, 1997 | Italy*NA* | Unselected patients (1983-1994) | Median duration = 10 (range 1-44) | ELISA (Reaads), ≥ 95th percentile 24 | 27/105 (aCL-IgG/IgM/IgA) |  |  |  |  |
| Pope *et al*, 2000 | Canada*NA* | Samples from hospital serum data bank | Mean duration = 5.2 years | ELISA (NA), > 15 UI | 3/63 (aCL-IgG/IgM) |  |  |  |  |
| Regéczy *et al*, 2000 | Hungary*NA* | Random selection of patients (1997-1998) | NA | LA: thromboplastine timeELISA (homemade), > mean ± 3 SD of controls | 10/43 (aCL-IgG/IgM) |  |  |  |  |
| Renaudineau *et al*, 2001 | Israel*NA* | Non-selected patients | NA | ELISA (homemade), mean ± 3 SD of controls | 55/478 (aCL-IgG) |  |  |  |  |
| Tektonidou *et al*, 2000 | Greece*NA* | Consecutive patients | NA | LA: thromboplastine timeELISA (homemade), > mean ± 3 SD of controls (100 UI) | 0/30 (aCL-IgG/IgM)0/30 (anti-β2GP1-IgG) |  |  |  |  |
| Touré *et al*, 2013 | Senegal*NA* | Cross-sectionnal study (2009-2010) | NA | LA: thromboplastine timeELISA (Diagnostica Stago laboratories), 40 UI/mL | 23/40 (aPL)2/40 (LA)7/40 (aCL-IgG/IgM)20/40 (anti-β2GP1-IgG/IgM) |  |  |  |  |
| Wielosz *et al*, 2009 | Poland*NA* | Consecutive patients (2005-2007) | 6.2 ± 6.0 yr\* | ELISA (Hycor Incorporation) for aCL, 20 UI/mLELISA (Euroimmun) for anti-β2GP1, 15 UI/mL | 28/56 (aCL-IgG/IgM+anti-β2GP1-IgG/IgM) |  |  |  |  |

\*mean ± standard deviation, NA: not available, ELISA: enzyme-linked immunosorbent assay, LA: lupus anticoagulant, aCL: anti-cardiolipin antibodies, anti-β2GP1: anti-β2GP1 antibodies