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Adjusted Global Antiphospholipid Syndrome Score (aGAPSS) is useful to predict relapses in patients with retinal vein occlusion

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Abstract

Background: A significant proportion of patients with retinal vein occlusion (RVO) are antiphospholipid antibodies (aPL) carriers. Relapsing disease occurs in nearly 10% of cases and the role of aPL has not been established. The adjusted global antiphospholipid syndrome score (aGAPSS) was developed to assess the risk of clinical events in aPL carriers and its role in the management of RVO patients is unknown.

Objective: To analyze the values of aGAPSS in a large cohort of patients with RVO and population-based controls, and to assess its usefulness to predict RVO relapses.

Methods: Case-control study of RVO patients and population-based controls of similar age and sex. We have assessed and compared the aPL profile and the aGAPSS score in patients with and without relapsing disease and controls.

Results: Four-hundred and seventy-two RVO patients and 346 controls were included. Fifty-seven RVO patients had antiphospholipid syndrome (RVO-APS). Of them, 75.4% had a high-risk profile compared to 3% in controls (p=0.0001). The median aGAPSS values were 8 [7-13], 3 [1-4], and 3 [0-4], in RVO-APS, RVO no-APS, and controls. Nineteen patients had had a recurrence of RVO before inclusion and 8 during the follow-up. APS was more prevalent in relapsing patients. In the adjusted multivariable regression model, the best predictor for RVO recurrence during the follow-up was an aGAPSS score ≥6 (OR 5.5, CI95% 1.3-23.7; p=0.023).

Conclusions: In patients with RVO, once the control of vascular risk factors has been optimized, the aGAPSS might help to identify those at risk of relapsing disease.

Keywords

Retinal vein occlusion; Antiphospholipid antibodies; Antiphospholipid syndrome; Relapses; Adjusted global antiphospholipid syndrome score.

1. Introduction

Retinal vein occlusion (RVO), either central or branch type, is a common cause of visual loss and it may mainly be considered a manifestation of the atherosclerotic process [1]. Thus, it has been related to increased cardiovascular morbidity and mortality in observational studies and metaanalyses [2,3]. Aging, classic cardiovascular risk factors, and local factors such as open-angle glaucoma have been involved as the main etiopathogenic factors. Furthermore, in some patients, acquired and genetic thrombophilia may also play a role in this retinal disorder [4,5].

We recently showed that antiphospholipid antibodies (aPL) were more prevalent in patients with RVO than in population-based controls, and a high-risk aPL profile (lupus anticoagulant or triple-positive serology) was frequent in patients with RVO and antiphospholipid syndrome (APS)[6].

RVO relapses have been reported to occur in about 7-10% of cases, and several predisposing factors have been involved, mainly classic cardiovascular risk factors, alcohol, and in some reports, hyperhomocysteinemia [7-9].

The adjusted global antiphospholipid syndrome score (aGAPSS) is based on a quantitative score and includes a combination of two classic vascular risk factors (hypertension and hyperlipidemia) and three aPL (lupus anticoagulant [LA], anticardiolipin antibodies [ACL] and anti-β_2 anti glycoprotein I antibodies [antiβ_2GPI])[10]. It was originally developed to identify patients with systemic lupus erythematosus (SLE) at greater risk of thrombotic events and/or pregnancy morbidity [11]. We recently published its usefulness to predict obstetric outcomes also in aPL carriers [12], and several reports have addressed its utility to predict thrombotic events [10,13,14]. However, to date, the role of aGAPSS in RVO has not been explored.

Taking into account these considerations we aimed to a) analyze the values of the aGAPSS in a large cohort of patients with RVO and population-based controls of similar age and gender, and b) assess the usefulness of aGAPSS as a tool to predict relapses in our cohort of patients with RVO.

2. Subjects and Methods

2.1 Participants and study protocol

We carried out a case-control study of all consecutive patients diagnosed with RVO ("Valdecilla cohort") from December 2008 to December 2021 and a randomly selected sample of controls of

similar age and gender including in a population-based prospective cohort in the same geographic area. RVO patients were studied at the University Hospital Marqués de Valdecilla, a tertiary-care center that serves as a reference hospital for a population of 350.000 inhabitants in northern Spain. All consecutive patients diagnosed with RVO at the Department of Ophthalmology, according to clinical, fundoscopic, and angiographic criteria, were assessed at our Internal Medicine outpatient clinic. The control group includes subjects who were taking part in a prospective population-based cohort, the Camargo cohort set up with postmenopausal women and men aged 50 years or older who attended a primary care center in Northern Spain for medical reasons or for their regular health examination, whichever happened first. Full details of this cohort have been previously reported [15,16]. Exclusion criteria for controls were the presence of any hematological or connective tissue disorder or active neoplasia. None of the participants were receiving contraceptives or hormone replacement therapy.

The Sapporo (Sydney revision) APS Classification Criteria were used to diagnose APS [17]. Although there is currently no high-quality evidence to support the use of antiplatelet drugs in the management of RVO [6,18], our RVO patients with APS (RVO-APS) were usually treated with aspirin. In those who had suffered previous vascular or thrombotic events or were younger than 50 years or did not have vascular risk factors, anticoagulation with acenocoumarol was prescribed. In non-anticoagulated patients and controls with positive aPLs, we recommended low-molecular-weight heparin prophylaxis in high-risk situations for thrombosis (immobilization for >24 h and major surgical procedures). The control group without RVO was set up between April 2013 and September 2018. All the participants were screened for acquired thrombophilia (serum anticardiolipin [ACL] and anti-β2 glycoprotein I antibodies [Aβ2GPI] and LA).

RVO patients were on optimized therapy for high blood pressure, dyslipidemia, or diabetes mellitus, according to the current guidelines, and quitting smoking was advised. Those patients with folic acid or vitamin B12 deficiency or serum hyperhomocysteinemia (defined as homocysteine levels >15 µmol/L) were treated with oral folic acid and vitamin B12 supplements. Antiplatelet therapy was prescribed according to a recent position statement, that recommends considering long-term aspirin administration for primary prevention of cardiovascular disease in patients with RVO and high or very high vascular risk [18].

Anticoagulation was considered in patients with atrial fibrillation, vascular events outside the retinal vessels, or high-risk thrombophilia (APS and/or major genetic thrombophilia).

The information collected from individual cases has been completely anonymized and the study was approved by the Ethics Committee of Cantabria (internal code: 2018.279) and participants gave written informed consent.

2.2 Variables analyzed and work definitions

Data were collected using a prespecified standardized questionnaire, in a computerizing database. The following baseline variables were analyzed: age, sex, body mass index (BMI), current tobacco use, alcohol intake (> 20 g per day), hypertension (equal or > 140/90 mm Hg or being on antihypertensive agents), diabetes mellitus (according to the ADA criteria) [19], dyslipidemia (serum total cholesterol > 230 mg/dL or triglyceride levels >150 mg/dL or receiving lipid-lowering drugs), history of ischemic heart disease, stroke, peripheral arterial disease or thromboembolic disease outside the retinal vessels, type of RVO (central or branch-type), family history of venous thromboembolism and prescribed treatments.

Relapse was defined as a new episode of RVO confirmed by an experienced ophthalmologist according to clinical, fundoscopic, and angiographic criteria.

2.3 Laboratory data

Blood samples were obtained from all the participants in the morning after a requested 12-hour overnight fast, within the week following the first outpatient visit. Routine biochemical parameters were measured by standard automated methods in an ADVIA 2400 Chemistry System autoanalyzer (Siemens).

Serum homocysteine was initially determined using a BN® II nephelometer (Siemens). After June 2012, it was assessed by chemiluminescence (Immulite, Siemens). Hyperhomocysteinemia was considered if serum levels were >15 µmol/L.

In the case of coagulation parameters, blood samples were collected in vacutainer tubes containing NaCitrate 3.2% in 1/9 proportion. After centrifugation (2500 rpm), 1 ml aliquots were stored at −30 °C. The hypercoagulability study included platelet count, prothrombin time, activated partial thromboplastin time, fibrinogen, LA, ACL, and Aβ2GPI. LA was determined with the hexagonal phase phospholipid neutralization test by a coagulometric method and Staclot® LA reagent (Diagnostica Stago). Serum ACL and Aβ2GPI antibodies were determined by ELISA and AESKULISA® reagent (Diagnostics). In patients or controls whose initial test was positive for aPLs, we performed a second test after 12 weeks. When medium or high-titers of APLs were detected, the test was considered positive (low-titer aPLs were considered negative). In

participants whose initial and second tests showed some discrepancies, we perform the third test after another 12 weeks, computing its results. In cases with positive aPLs, antinuclear antibodies (ANA) test was performed by indirect immunofluorescence. A titer >1/160 was considered a positive result. High-risk serology has been defined, according to the EULAR recommendations for the management of APS in adults, as the presence (in 2 or more occasions at least 12 weeks apart) of lupus anticoagulant, or of double (any combination of lupus anticoagulant, ACL antibodies or Aβ2GPI antibodies) or triple (all three subtypes) aPL positivity, or the presence of persistently high aPL titers [20]. The remainder of the study included protein C, protein S, antithrombin and FVQ506 (FV Leiden), and prothrombin 20210A mutation. A genetic thrombophilia study was performed on all patients from December 2008 to December 2015. Thereafter, since genetic thrombophilia had been found to play a minor role in RVO pathogenesis, it was determined only in patients younger than 50 years or in those without vascular risk factors at the time of RVO diagnosis [5,6].

2.4 Ultrasound study

To assess the presence of atheromatous plaques in the carotid and vertebral arteries, in RVO patients, a Doppler ultrasound (US. B-mode, color Doppler, and spectral mode, General Electric, Logic®) of the supra-aortic trunks was performed.

2.5 Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median and interquartile range and compared with the Student's t-test, Mann–Whitney U test, and one-way ANOVA or Kruskal-Wallis test with Bonferroni post-hoc test according to the distribution of data. Categorical variables were presented as numbers and percentages and compared using the chi-squared test or the Fisher exact test as appropriate. A multivariable backward stepwise logistic regression model adjusted for age, sex, BMI, smoking, glaucoma, classic vascular risk factors, and aGAPSS (<6 or ≥6 points) was built using relapsing RVO during the follow-up period as the dependent variable. IBM SPSS 28.0 was used for the statistical analyses (Armonk, NY: IBM Corp). A two-sided p-value <0.05 was considered statistically significant in all the calculations.

3. Results

3.1 General features

We analyzed 472 consecutive patients with RVO during the study period. Of them, 320 (67.8%) were of branch type (314 temporal and 6 nasal) and 152 (32.2%) were central RVO. Fifty-seven patients had APS (RVO-APS group); 42 (73.7%) had branch-type and 15 had central RVO (26.3%). The correspondent figures for RVO no-APS patients were 278 (67%) and 137 (33%) respectively (p=0.31). Three hundred and forty-six population-based controls were also included in the study. None of the participants had a family history of thrombophilia or systemic lupus erythematosus. Table 1 shows the baseline epidemiological features and laboratory parameters of the study groups. Genetic thrombophilia was observed in 2 of 26 (7.7%) RVO-APS patients (protein S deficiency [n=1] and antithrombin deficiency [n=1] and 36 of 232 (15.5%) with RVO-noAPS (prothrombin 20210A mutation [n=11], protein S deficiency -n=9- and antithrombin deficiency -n=7-, protein C deficiency -n=5- and FV Leiden -n=4-). Carotid and vertebral doppler ultrasound were available for 427 RVO patients and 225 (52.7%) had atherosclerotic plaques. Antiplatelet or anticoagulant therapy before and after the initial assessment in our outpatient clinic was shown in Supplementary Table 1. Data regarding previous thrombotic events outside the retinal vessels (including stroke, ischemic cardiac disease, and other thromboembolic diseases) were as follows: RVO-APS, n=11 (19.3%); RVO-noAPS, n=58 (13.9%) and controls, n=41 (11.9%). There were no significant differences among groups. The median follow-up of the overall RVO cohort was 61 (31-111) months.

3.2 aPL profile

Table 2 shows the serological aPL profile in patients with RVO-APS and controls. It is worth mentioning that 43 of 57 (75.4%) RVO-APS subjects had the “high-risk” pattern, which includes any of the following: the presence of LA, the presence of double (any combination of LA, ACL or Aβ2GPI antibodies) or triple (all three subtypes) aPL positivity. In about 3% of the population-based controls LA was detected (p=0.0001).

3.3 aGAPSS

Figure 1 shows the mean aGAPSS values in these study groups. The median aGAPSS values were 8 (7-13), 3 (1-4), and 3 (0-4), in RVO-APS patients, RVO no-APS group, and controls. The aGAPSS was categorized into three risk categories: low (<6 points); medium (between 6 and 11

points) and high-risk ≥12 points) [12]. The percentage of RVO patients and control subjects included in each of these aGAPSS categories is shown in Supplementary Figure 1.

3.4 RVO relapses

Nineteen patients had had an RVO relapse before the study onset. Eight patients (1.7%) had RVO recurrence during the follow-up period, once cardiovascular risk factors were optimized and antiplatelet or anticoagulant agents were started when indicated according to the current guidelines. One of them had had a relapse before inclusion (he was a 65-year-old man with glaucoma and APS). Table 3 shows the main epidemiological characteristics and laboratory parameters of patients with relapsing RVO (before inclusion and during the follow-up) compared to those who did not. We found that there were no significant differences in the main cardiovascular risk factors, whilst serum homocysteine levels were lower in patients who experience recurrences during the follow-up.

The main features of patients who suffer an RVO relapse during the follow-up are shown in Supplementary Table 2, The aPL profile of RVO patients and those with relapsing disease during the follow-up was shown in Table 4. APS was more prevalent in relapsing patients as well as a high-risk aPL profile. The distribution of the different aGAPSS categories in single RVO episodes and those with relapsing disease (before inclusion and during the follow-up) is shown in Figure 2. Noteworthy, patients with relapses during the follow-up have higher aGAPSS values (≥6) than the other groups analyzed: 37.5% vs. 9.6% in non-relapsing RVO (p=0.038), and 11.1% (p=0.28) in patients with previous relapses. Figure 3 shows the Kaplan-Meier plot showing the cumulative relapses in both aGAPSS groups (<6 and ≥6 points). The log-rank test was significant (p=0.003).

In the multivariable regression model, adjusted for age, sex, smoking, BMI, glaucoma, dyslipidemia, hypertension, type 2 diabetes mellitus, and aGAPSS, the best predictor for RVO recurrence was an aGAPSS score ≥6 (OR 5.5, CI95% 1.3-23.7; p=0.023).

4. Discussion

We have shown, for the first time, that the aGAPSS could be useful to predict the risk of recurrence of RVO. Besides, APS was diagnosed in half of the patients with relapsing retinal disease, and they frequently had a high-risk aPL profile compared to non-relapsing subjects.

Medical conditions and risk factors underlying relapsing RVO have been analyzed in a few reports, suggesting that about 10% of patients who have a single episode will go on to relapse. In this sense, Dodson et al. [9] analyzed 61 patients (26 with central and 35 with branch-type RVO) with single RVO and 17 with recurrent disease. They found that hyperlipidemia, hypertension (88% vs 48%, p<0.01), and alcohol intake >7g/day (47% vs. 13%; p<0.01) could be risk factors for relapsing RVO. Although the percentage of hyperlipidemia (47% vs. 33%) was higher in cases of recurrence, the difference was not statistically significant. Lower serum HDL-cholesterol levels (1.24±0.3 vs. 1.46±0.3 mmol/L; p<0.02) and increased systolic blood pressure (175±30.2 vs. 156±26.4 mmHg; p<0.01) were also observed in relapsing patients compared to single RVO.

A cross-sectional study that compared 17 patients with recurrent central RVO and 30 subjects suffering from a single episode, found dyslipidemia and hyperhomocysteinemia (fasting and postmethionine) to be independent risk factors for the occurrence of central RVO relapses [8]. The authors did not find any difference neither in the aPL profile nor the prevalence of genetic thrombophilia (Factor V Leyden and factor II mutations) between patients with and without relapses.

Noteworthy, we found the lowest serum homocysteine levels in patients who experience an RVO relapse during the follow-up. This finding could have some explanations. Firstly, raised baseline serum homocysteine levels in RVO patients prompted us to initiate therapy with folic acid and vitamin B_{12}, and this fact, along with the tight control of cardiovascular risk factors, could be associated with fewer relapses during the follow-up, as observed in our study. Secondly, as shown in Table 3, RVO patients who had experienced a relapse before the study onset had had more cardiovascular events than those who had a new recurrence during the follow-up. This may explain, at least in part, the lower values of serum homocysteine levels, since high levels of this amino acid have been mainly related to cardiovascular disease. Furthermore, patients with a previous relapse had also more frequent glaucoma, a well-known risk factor for RVO, along with some traditional cardiovascular risk factors, such as smoking. Besides, in the latter group, there was a higher prevalence of high-risk APL serology. Thus, it seems that in patients with a relapsing RVO episode during the follow-up period, the role of the aPL profile is more relevant than that of major cardiovascular risk factors or local factors (glaucoma), since the control of these factors has been optimized once the follow-up was initiated.

Fernández-Mosteirin et al. [13] confirmed the external validity of the aGAPSS to predict thrombosis, in a retrospective cohort study of 319 patients with APS and/or autoimmune diseases

over a mean period of 52 months. Furthermore, higher aGAPSS values have been observed in young patients with APS and acute myocardial infarction [14]. In the same line, a study of 379 APS patients from the Antiphospholipid Syndrome Alliance for Clinical Trials and International Networking (APS ACTION) Clinical Database and Repository, presented with arterial and/or venous thrombosis, found significantly higher aGAPSS values were observed in those with recurrent thrombosis compared to patients without relapses [10]. In this regard, we found that the highest aGAPSS values corresponded to patients with relapses, mainly new RVO episodes during the follow-up period.

We found that APS was more frequent in patients with relapsing retinal disease (50% had APS) as well as a high-risk aPL pattern. This profile has been associated with a higher risk of thrombosis recurrence in APS patients [21].

aGAPSS has also been shown to be useful in predicting cardiovascular disease in subjects with aPLs. Thus, in a recent study, aGAPSS detected 63% of cardiovascular events and was associated with a 2.5-fold increased probability of CV disease in these subjects [22]. Since classic vascular risk factors and thrombophilia have been involved as etiopathogenic factors in RVO, we have explored the potential usefulness of the aGAPSS in the assessment of the risk of relapsing disease. In fact, aGAPSS includes the main cardiovascular risk factors that have been related to RVO recurrence, such as arterial hypertension and hyperlipidemia, as well as the aPL profile. Moreover, aGAPSS considers both the aPL profile and traditional cardiovascular risk factors. Although no single aPL positivity and traditional cardiovascular risk factor were found to be independently associated with an increased risk of relapsing RVO, when computed in a scoring system, both factors contribute to the risk stratification as part of the variables included in the aGAPSS.

In addition to the aGAPSS, there is another score to predict the thrombotic risk in patients with APS, the aPL score [23]. Although there has been reported that aPL score could have a greater ability than GAPSS to predict thrombotic events [24], in the present study we have used the aGAPSS due to its simplicity to use in clinical settings and, as stated, because of it includes the main cardiovascular etiopathogenic risk factors for RVO.

5. Limitations

Our study has some limitations. Firstly, those inherent to the design of a case-control study. Secondly, the number of RVO recurrences during the follow-up was small, although this finding may be most probably related to the tight control of the patients in our clinic, and could also be seen as a strength of the study. Thirdly, we have not addressed either the impact of non-criteria aPL or the persistence of aPL over time.

6. Conclusions

In conclusion, according to our data, once cardiovascular risk factors (hypertension, dyslipidemia, and type 2 diabetes mellitus) and hyperhomocysteinemia have been controlled, following the current clinical practice guidelines, an aGAPSS≥6 is associated with a 5.5-fold increased risk of recurrent RVO. Thus, aGAPSS might help to stratify RVO patients based on the likelihood of developing recurrent disease. This strategy may guide the pharmacological therapy for high-risk patients, such as the intensification of antiaggregant treatment, anticoagulation, or even the use of hydroxychloroquine, as occurs in SLE patients, to reduce the risk of thrombotic events. Larger studies are needed to deepen our understanding of the knowledge of RVO relapses and to improve the therapeutic scheme for this ophthalmological complication.

Declaration of competing interest

The authors have no competing interest to declare regarding this paper.

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Tables and Figures

Table 1. Baseline epidemiological features and laboratory parameters of the study participants.

Variable	RVO-APS (N=57)	RVO-noAPS (N=415)	Controls (N=346)	p^1	p^2	p^3
Age (yrs.), *mean±SD*	69.7±12.9	67.1 ± 12.8	68.6 ± 8.8	0.32	0.99	0.21
Sex (women), *n (%)*	26 (45.6)	197 (47.5)	183 (52.9)	0.79	0.31	0.14
Classic CVRF, *n (%)*	50 (87.7)	375 (90.4)	255 (73.7)	0.53	0.022	0.0001
Type 2 diabetes mellitus, *n (%)*	17 (29.8)	95 (22.9)	53 (15.3)	0.25	0.007	0.009
Smoking, *n (%)*	7 (12.3)	60 (14.5)	42 (12.1)	0.66	0.98	0.35
Alcohol intake, *n (%)*	10 (17.5)	80 (19.3)	50 (14.3)	0.76	0.54	0.10
Hypertension, *n (%)*	40 (70.2)	298 (71.8)	182 (52.6)	0.79	0.013	0.0001
Dyslipidemia, *n (%)*	39 (68.4)	270 (65.1)	171 (49.4)	0.62	0.008	0.0001
Hyperhomocysteinemia, *n (%)*	38 (66.7)	183 (45.1)	63 (30.7)	0.002	0.0001	0.001
Glaucoma, *n (%)*	12 (21.1)	77 (18.9)	20 (7)	0.69	0.001	0.0001
Ischemic heart disease, *n (%)*	4 (7)	24 (5.8)	21 (6.1)	0.76	0.77	0.87
Peripheral arterial disease, *n (%)*	3 (5.3)	8 (1.9)	5 (1.4)	0.14	0.09	0.61
Cerebrovascular disease, *n (%)*	5 (8.8)	24 (5.8)	14 (4)	0.38	0.17	0.27
DVT/PE, *n (%)*	2 (3.5)	10 (2.4)	6 (1.7)	0.65	0.32	0.52
Atrial fibrillation, *n (%)*	0 (0)	42 (10.2)	24 (6.9)	0.046	0.23	0.12
Abnormal carotid US, *n (%)*	28 (57.1)	197 (53.1)	-	0.51	-	-
BMI (Kg/m²), *mean±SD*	29.1±5.0	28.9 ± 4.9	28.9 ± 4.5	0.99	0.99	0.99
SBP (mmHg), *mean±SD*	149.8±24.6	147.3 ± 21.5	137.8 ± 17.7	0.99	0.0001	0.0001
DBP (mmHg), *mean±SD*	83.6±10.9	84.4 ± 10.2	77.2 ± 9.5	0.99	0.0001	0.0001
Total cholesterol (mg/dL), *mean±SD*	200.8±42.5	202 ± 40.1	199.1 ± 38.1	0.99	0.99	0.92
HDL (mg/dL), *mean±SD*	53.7±15.3	54.9 ± 15	57.2 ± 15.1	0.99	0.40	0.08
LDL (mg/dL), *mean±SD*	123.6±37.0	124 ± 35.2	120.3 ± 32.2	0.99	0.99	0.42
Triglycerides (mg/dL), *mean±SD*	121.5±51.1	113 ± 58.4	106.5 ± 40.8	0.99	0.23	0.22
Homocysteine (μmol/L), *mean±SD*	18.6±8.8	15 ± 5.5	14.6 ± 9.4	0.021	0.0001	0.001
Folic acid, *mean±SD*	8.5±4.0	9.1 ± 4.9	10.2 ± 4.4	0.99	0.18	0.009
Vitamin B_{12}, *mean±SD*	387.1±135.2	413.8 ± 188.1	422.7 ± 164.4	0.11	0.06	0.99

p^1: RVO-APS vs RVO-noAPS. p^2 RVO-APS vs controls. p^3 RVO-noAPS vs. controls

RVO: retinal vein occlusion; APS: antiphospholipid syndrome; CVRF: cardiovascular risk factors; DVT/PE: deep venous thrombosis/pulmonary embolism; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein. US: Ultrasound.

* Supra-aortic trunk US was performed in 427 RVO patients

Table 2. aPL profile of RVO-APS patients and population-based controls.

Parameter	RVO-APS (N=57)	Controls (N=346)
Lupus anticoagulant, *n (%)*	34 (59.6)	8 (2.8)
ACL, *n (%)*	24 (42.1)	-
- High titer, *n (%)*	*18 (75.0)*	-
- Medium titer, *n (%)*	*6 (25.0)*	-
- IgG, *n (%)*	12 (21.1)	-
- IgM, *n (%)*	15 (26.3)	-
Aβ$_2$GPI, *n (%)*	27 (47.4)	-
- High titer, *n (%)*	*21 (77.8)*	-
- Medium titer, *n (%)*	*6 (22.2)*	-
- IgG, *n (%)*	10 (17.5)	-
- IgM, *n (%)*	21 (36.8)	-
Single positive, *n (%)*	36 (63.2)	-
Double positive, *n (%)*	12 (21.1)	-
Triple positive, *n (%)*	9 (15.8)	-
High-risk serology, *n (%)*	43 (75.4)	8 (2.8)

ACL: anticardiolipin antibodies; Aβ$_2$GPI: anti-β$_2$ glycoprotein I antibodies.

Table 3. Baseline features and laboratory parameters in patients with single RVO episodes and relapsing disease (previous to inclusion and during the follow-up period).

Variable	Single RVO episode (N=445)	Previous relapsing RVO (N=19)	Follow-up relapsing RVO (N=8)	p^1	p^2	p^3
Age (yrs.), *mean±SD*	67.3±12.9	69.8±13.7	70.1± 9.7	0.99	0.99	0.99
Sex (women), *n (%)*	214 (48.1)	6 (31.6)	3 (37.5)	0.16	0.73	0.99
Classic CVRF, *n (%)*	401 (90.1)	17 (89.5)	7 (87.5)	0.93	0.57	0.99
Type 2 diabetes mellitus, *n (%)*	107 (24.0)	2 (10.5)	5 (62.5)	0.27	0.41	0.14
Smoking, *n (%)*	62 (13.9)	5 (26.3)	0 (0)	0.17	0.61	0.28
Alcohol intake, *n (%)*	88 (19.8)	2 (10.5)	0 (0)	0.55	0.36	0.99
Hypertension, *n (%)*	317 (71.2)	16 (84.2)	5 (62.5)	0.22	0.69	0.32
Dyslipidemia, *n (%)*	290 (65.2)	12 (63.2)	7 (87.5)	0.86	0.27	0.36
Hyperhomocysteinemia, *n (%)*	212 (48.5)	9 (50)	0 (0)	0.90	0.008	0.023
Glaucoma, *n (%)*	80 (18.2)	7 (38.9)	2 (25.0)	0.06	0.64	0.67
Ischemic heart disease, *n (%)*	25 (5.6)	3 (15.8)	0 (0)	0.09	0.99	0.53
Peripheral arterial disease, *n (%)*	11 (2.5)	0 (0)	0 (0)	0.99	0.99	-
Cerebrovascular disease, *n (%)*	25 (5.6)	3 (15.8)	1 (12.5)	0.09	0.38	0.99
DVT/PE, *n (%)*	12 (2.7)	0 (0)	0 (0)	0.99	0.99	-
Atrial fibrillation, *n (%)*	40 (9.0)	3 (15.8)	0 (0)	0.41	0.99	0.53
Abnormal carotid US, *n (%)*	208 (51.7)	11 (64.7)	6 (75)	0.29	0.28	0.99
BMI (Kg/m²), *mean±SD*	28.9±4.9	29.5±3.9	27.8±4.3	0.99	0.99	0.99
SBP (mmHg), *mean±SD*	147.7±22.2	146.4±17.3	145.3±17.8	0.99	0.99	0.99
DBP (mmHg), *mean±SD*	84.4±10.3	84.9±8.6	81.4±11.4	0.99	0.99	0.99
Total cholesterol (mg/dL), *mean±SD*	202.6±40.3	183.7±34.2	203.3±53.5	0.14	0.99	0.75
HDL (mg/dL), *mean±SD*	55.0±15.3	48.4±11.8	55.5±7.8	0.13	0.99	0.34
LDL (mg/dL), *mean±SD*	124.6±35.2	110.1±35.3	120.1±44.1	0.21	0.99	0.99
Triglycerides (mg/dL), *mean±SD*	113.5±51.3	133.3±41.3	99.9±38.5	0.99	0.99	0.99
Homocysteine (μmol/L), *mean±SD*	15.5±5.8	16.2±5.9	10.2±2.3	0.99	0.012	0.021
Folic acid, *mean±SD*	9.0±4.9	8.4±3.2	9.7±4.7	0.99	0.99	0.99
Vitamin B_{12}, *mean±SD*	403.8±181.4	429.5±154.9	579.7±403.3	0.99	0.99	0.99

p^1: single RVO episode vs previous relapsing RVO; p^2: single RVO episode vs. follow-up relapsing RVO; p^3: previous relapsing RVO vs. follow-up relapsing RVO

Table 4. aPL profile of RVO patients and those with relapsing disease during the follow-up.

Parameter	RVO (N=464)	Relapsing RVO during the follow-up (N=8)	p
Lupus anticoagulant, *n (%)*	32 (7.1)	2 (25.0)	0.11
ACL, *n (%)*	22 (4.8)	2 (25)	0.058
- IgG, *n (%)*	11 (2.4)	1 (12.5)	0.19
- IgM, *n (%)*	14 (3.0)	1 (12.5)	0.23
Aβ2GPI, *n (%)*	26 (5.6)	1 (12.5)	0.38
- IgG, *n (%)*	10 (2.2)	0 (0)	0.99
- IgM, *n (%)*	20 (4.3)	1 (12.5)	0.31
Single positive, *n (%)*	33 (7.1)	3 (37.5)	0.01
Double positive, *n (%)*	11 (2.3)	1 (12.5)	0.50
Triple positive, *n (%)*	9 (1.9)	0 (0.0)	0.37
High-risk serology, *n (%)*	40 (8.8)	3 (37.5)	0.03
APS, *n (%)*	53 (11.5)	4 (50)	0.009

ACL: anticardiolipin antibodies; Aβ2GPI: anti-β2glycoprotein I antibodies. APS: antiphospholipid syndrome

Figures

Figure 1. Mean aGAPSS values in the study groups.

Footnote: *Bars represent standard error.*

Figure 2. Distribution of aGAPSS categories in relapsing and no-relapsing RVO patients.

Figure 3. Kaplan-Meir plot showing the cumulative RVO recurrence according to the aGAPSS.

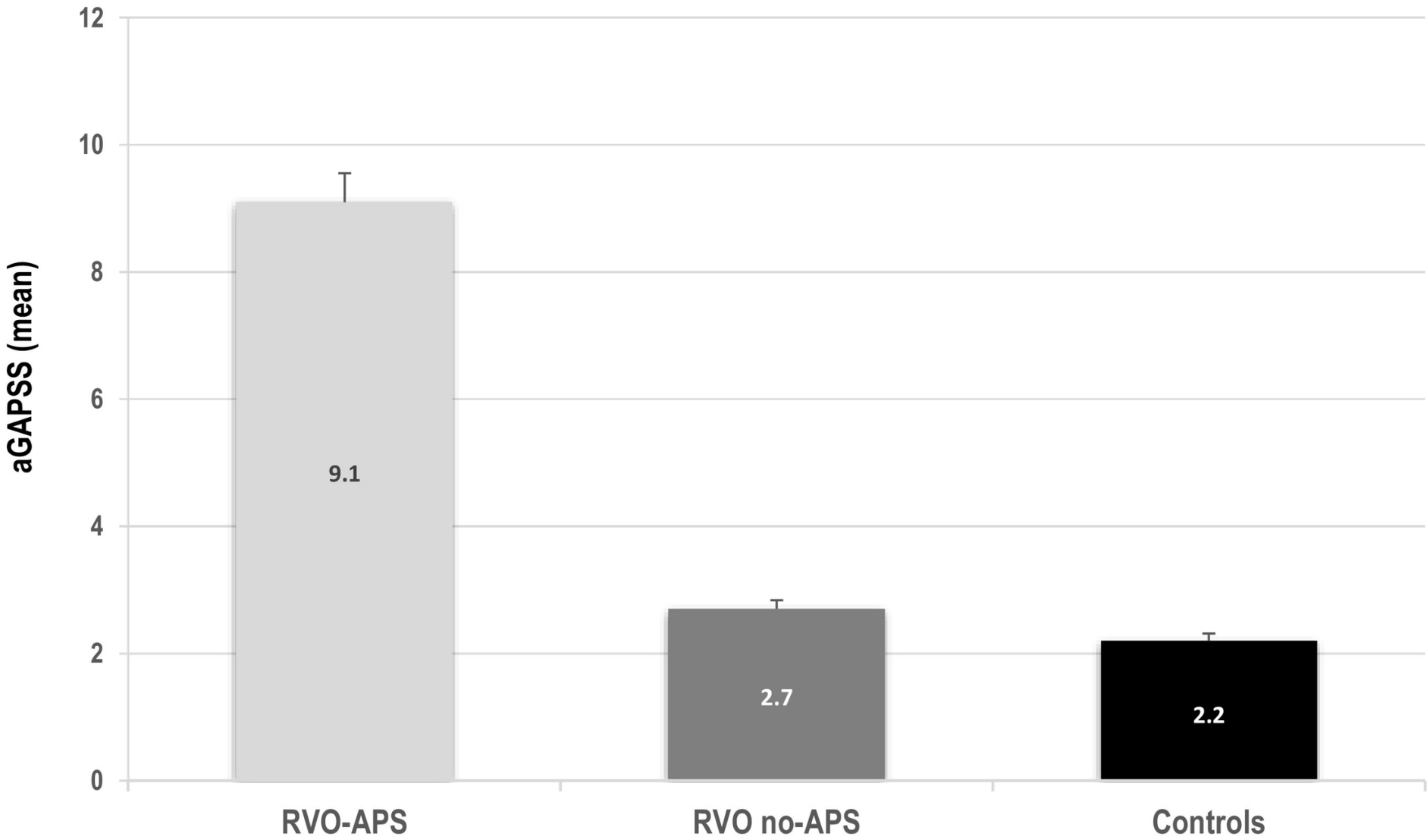

Figure 1

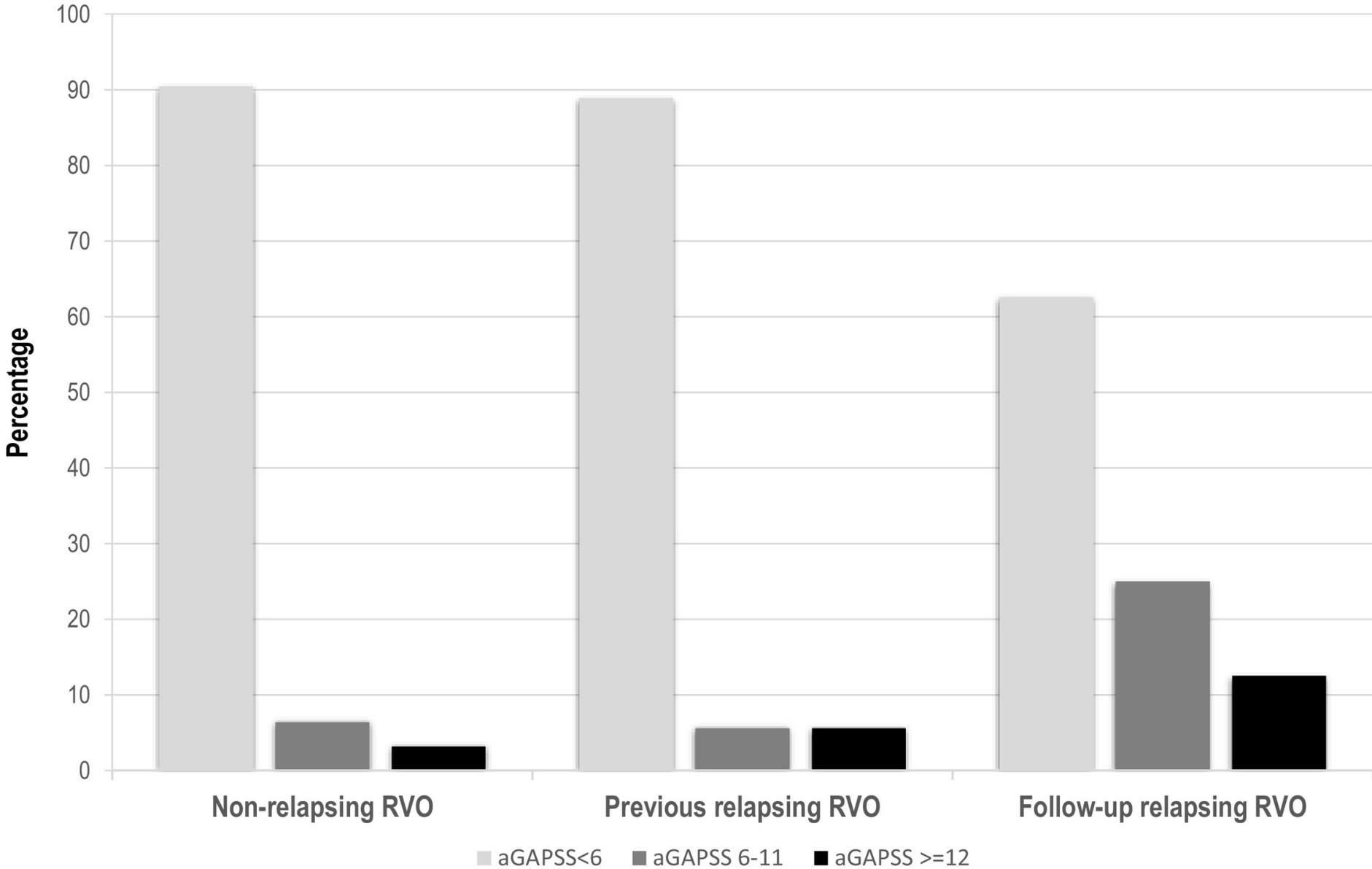
100
90
80
70
60
50
40
30
20
10
0
Percentage
Non-relapsing RVO
Previous relapsing RVO
Follow-up relapsing RVO
aGAPSS<6
aGAPSS 6-11
aGAPSS >=12

Figure 2

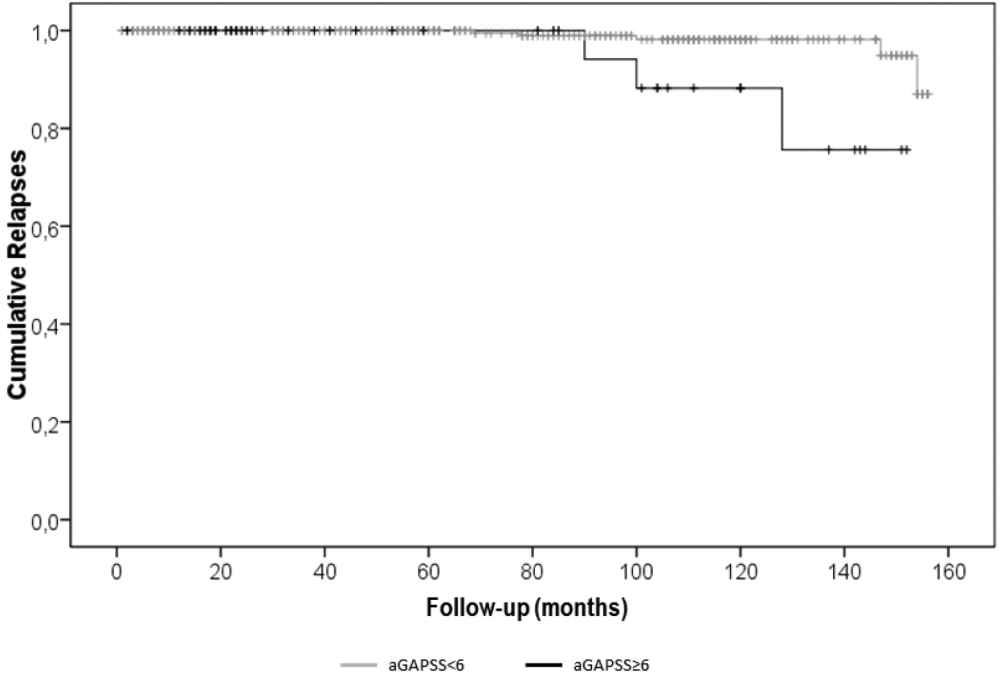
Cumulative Relapses
1,0
0,8
0,6
0,4
0,2
0,0
0
20
40
60
80
100
120
140
160
Follow-up (months)
aGAPSS<6
aGAPSS≥6

Figure 3