

## **Original study**

### **One Point Increase in the Initial Damage Measured by the Damage Index for Antiphospholipid Syndrome (DIAPS) Predicts Mortality in a Multi-Ethnic Group of Thrombotic Antiphospholipid Syndrome Patients**

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## **Abstract**

Introduction: Antiphospholipid syndrome (APS) leads to damage accrual that impairs long-term functional status. The Damage Index for Antiphospholipid Syndrome (DIAPS) captures the damage accrual in thrombotic APS, but it is not known whether it correlates with mortality. We aim to determine whether early damage and its kinetics predicts long-term mortality in thrombotic APS.

Methods: Retrospective analysis of 197 thrombotic APS patients (2006 Sydney classification criteria) followed at a tertiary centre in London up to 43 (median 10) years. The disease onset was the time the first thrombotic event related to APS was diagnosed. Early damage refers to damage present at six months after the disease onset. Early DIAPS increase refers to the increase of at least one point from the initial DIAPS within the first five of illness. We used logistic, uni and multivariable Cox regression models to analyse risk factors affecting mortality. Survival was analysed using the Kaplan-Meier method.

Results: The median age at APS onset was 40 (IQR 51-28) years, with a female (71%) and primary APS (66%) preponderance. Caucasian ethnicity was the most prevalent (72%), followed by Asian (10%), Afro-Caribbean (9%) and other (9%). Damage developed in 143 (73%) patients with a median DIAPS of 1 (IQR 2-0) at the last visit. Early damage was present in 69 (35%) patients. We identified 23 fatalities (12%). Deceased patients had higher last DIAPS ( $p=0.012$ ) but similar early DIAPS score ( $p=0.318$ ) compared to those who survived. Secondary APS (HR 3.07, 95%CI 1.32-7.12,  $p=0.009$ ), male gender (HR 3.14, 95%CI 1.35-7.33,  $p=0.008$ ) and age at APS onset  $\geq 40$  years (HR 5.34, 95%CI 1.96-14.53,  $p=0.001$ ) were risk factors for death. Early damage was not associated with death (HR 1.65, 95%CI 0.73-3.78,  $p=0.231$ ). Early DIAPS increase ( $n=53/181$ , 29%) was

associated with death (HR 5.40, 95%CI 2.33-12.52,  $p < 0.001$ ), even after adjusting individually for APS category (secondary,  $p < 0.001$ ), gender (male,  $p < 0.001$ ) and age at APS onset ( $\geq 40$  years,  $p = 0.006$ ). Having a first arterial event was associated with early damage ( $p < 0.001$ ), but not with early DIAPS increase ( $p = 0.539$ ) nor with the risk of death ( $p = 0.151$ ).

Conclusion: An increase of at least one point on DIAPS in the first five years after disease onset, but not early damage, predicts of mortality regardless of the nature of the first thrombotic event, gender, APS category and age.

## Introduction

Thrombotic antiphospholipid syndrome (APS) is an acquired autoimmune thrombophilia characterized by recurrent venous, arterial and/or microvascular thrombosis in the presence of persistently positive antiphospholipid antibodies (aPL) (1). Lifelong anticoagulation with warfarin or alternative vitamin K antagonist remains the standard of care (2), but despite optimal treatment patients remain at risk of recurrent thrombosis (3). The relapsing nature of this condition leads to damage accrual in almost one third of patients (4) with long-term survival and functional status impairment (5,6).

Initial attempts to capture APS related damage used the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index (SDI) (7). The SDI score as a surrogate marker of damage was associated with increased mortality in APS patients (5). However, the SDI missed some key features of APS and could, therefore, underestimate its damage (8). In 2015, Amigo and colleagues (9) published a new scoring instrument, the damage index for APS (DIAPS), specifically designed to overcome some of the SDI limitations with regard to assessing the full damage picture of thrombotic APS. The DIAPS is a 38-item score that has demonstrated content, criterion and construct validity as well as a significant positive high correlation with impaired health-related quality of life in Latin Americans (9,10).

In systemic lupus erythematosus (SLE), the presence of early damage defined as at least one item scored in the SDI at six months is associated with a higher rate of mortality within 10 years (25% vs. 7.3%; log-rank  $p < 0.001$ ) (11). The authors found this of clinical utility as one could identify the patients with

increased mortality risk right at the beginning of follow-up. No similar fact is known for thrombotic APS. Only a few studies have investigated factors associated with damage development, its quantification and kinetics in APS (4,5,9,10,12). Moreover, there has been no correlation between the damage acquisition measured by the DIAPS with mortality after its initial development and validation. Torricelli et al (12) recently showed that primary APS (PAPS) and APS related to SLE have a different pattern of damage acquisition measure by the DIAPS, but no correlation with mortality was also made.

In this study, we aim to determine whether early damage and its accrual kinetics as measured by the DIAPS predicts long-term mortality in thrombotic APS. We also sought to analyse the role of different clinicodemographic features, including age, ethnicity, type of first thrombotic event and type of APS, in damage acquisition measured by DIAPS and mortality.

## **Material and Methods**

### Patients

We carried out a retrospective analysis of all medical records of 197 thrombotic APS patients attending the Rheumatology and/or Haematology clinics at University College of London Hospital until December 2019. We reviewed patients' files up to 43 years. We included patients with PAPS as well as thrombotic APS secondary to other autoimmune condition (Secondary APS, [SAPS]). All patients fulfilled the 2006 Sydney classification criteria (1). aPL positive patients without thrombotic events were not included.

### Data collection and Definitions

Patients' demographic and clinical characteristics, as well as laboratory data were obtained through the detailed analysis of all electronic and paper files. The disease onset was the time the first thrombotic event related to APS was diagnosed. Clinical events were accessed beginning with the disease onset and confirmed using information present in all available medical exams. DIAPS was used to measure damage accrued since the disease onset. We have only considered clinical events that lasted for at least 6 months or have resulted in permanent harm to be considered as damage. In the present study we used the standard definitions for each item as outlined in the DIAPS glossary (9). The first damage assessment was done at six months after disease onset. We defined early damage whenever a patient presented at least one item scored at six months after disease onset. DIAPS was then calculated yearly, and all collected data was recorded in an individual patient sheet. Early DIAPS increase (delta-

DIAPS) refers to the increase of at least one point from the initial DIAPS score within the first five years after the disease onset (i.e., DIAPS increased from 0 to 1; from  $\chi$  to  $\geq \chi+1$ ).

Only data obtained as part of routine clinical management were included and only pooled data with no patient identifiable information are reported in this paper. Thus, research ethics approval was not required.

### Statistical analysis

Statistical analysis was performed using STATA® version 16. We compared groups of patients using Pearson's chi-squared test or Fischer exact test for categorical variables, and T-test or Mann-Whitney U test for continuous numerical variables. We used logistic, univariable and multivariable Cox regression models to analyse risk factors affecting mortality. Survival curves were obtained using the Kaplan-Meier method. Patients were censored if they were lost to follow-up or reached the end of the study. DIAPS score is shown as median (interquartile range [IQR]). For comparison purposes with similar studies, DIAPS values will also be presented as mean  $\pm$  standard deviation (SD). Significance level was defined at 0.05.

## Results

### Demographic and Disease characteristics

One hundred and ninety-seven patients were identified, of those 71.1% were female and 65.9% had PAPS. One hundred and twenty-eight patients (65%) had no early damage while 69 patients (35.0%) had at least one DIAPS item scored in the first six months after the disease onset. **Table 1** shows a comparison of the demographic, clinical and laboratory characteristics between the two groups. The median age at APS onset was 40 (IQR 51-28) years, and patients were followed for a median of 10 (IQR 17-6) years. Caucasian ethnicity was the most prevalent (71.6%), followed by Asian (9.8%), Afro-Caribbean (9.3%) and other (9.3%). APS patients with early damage had comparable gender distribution (female, 69.6% vs. 71.9%,  $p=0.733$ ), median age of disease onset (40, IQR 49 – 29 years vs. 40, IQR 53 – 27.5 years,  $p=0.526$ ) and median time of follow-up (9, IQR 15 – 6 years vs. 11.5, IQR 17.5 – 7 years,  $p=0.181$ ) compared to those with no early damage. In contrast, the proportion of patients with SAPS was higher in patients with early damage compared to those without early damage (43.5% vs. 28.9%,  $p=0.039$ ).

Venous thrombosis was the most frequent initial thrombotic manifestation (58.8%), followed by arterial (44.2%) and microvascular thrombosis (2.5%). The type of the first clinical event differed significantly between the two groups. Patients with early damage had higher proportion of arterial events at onset (73.9% vs. 28.1%,  $p<0.001$ ) compared to patients with no early damage who had higher proportion of venous events at disease onset (72.7% vs. 33.3%,  $p<0.001$ ). Most patients (79.2%) were lupus anticoagulant (LA) positive. Anticardiolipin (ACL) antibodies, anti-B2-Glycoprotein I (B2GPI) antibodies and triple positivity

were found in 59.4%, 52.8% and 6.6% of patients, respectively. We observed no difference in the frequencies of any aPL profile (LA, 82.6% vs. 77.3%,  $p=0.385$ ; ACL, 59.4% vs. 59.4%,  $p=0.995$ ; B2GPI, 50.7% vs. 53.9%,  $p=0.670$ ; and triple-positivity, 5.8% vs 7.0%,  $p=1.000$ ) between patients with and without early damage.

### Damage kinetics and Early damage increase

DIAPS was measured at the first six months (DIAPS-0), and at the fifth, 10th, 15th, 20th, 25th, 30<sup>th</sup>, 35<sup>th</sup> and 40<sup>th</sup> year after the diagnosis of APS. The results are shown in **Table 2**. Early DIAPS scored low values in the whole group (median 0, IQR 1-0; mean  $0.49 \pm 0.82$ ). The highest score was 5 ( $n = 1$ ). Accrual damage developed in 143 patients (72.6%). The proportion of patients with any damage (DIAPS  $\geq 1$ ) gradually increased from around one third at the first evaluation, to more than 60% at year 15 and beyond. DIAPS scored higher values at the end of follow-up (median 1, IQR 2 – 0; mean  $1.59 \pm 1.72$ ). The highest score was 11 ( $n = 1$ , 0.5% of patients). At the last visit, 54 patients (27.4%) were free of damage. It is noteworthy that all patients followed for more than 30 years developed damage. The final DIAPS score was significantly higher in patients with early damage compared to those without early damage (2, IQR 3 -1 vs. 1, IQR 2 – 0,  $p<0.001$ ) (**Table 1**). Accordingly, compared to patients with no early damage, patients with early damage had higher prevalence of DIAPS  $\geq 3$  in the last evaluation (30.4% vs. 14.1%,  $p=0.006$ ) and with a significantly lower median time to event (4, 11 – 2 years vs. 11.5, 20 – 6 years,  $p=0.028$ ) (**Table 1**).

Regardless of the presence of early damage, 29.3% of patients (53 out of 181 eligible patients with at least five years of follow-up) had an increase of at least

one point in the damage score in the first 5 years after the disease onset (delta-DIAPS). These groups are compared in **Table 3**. Patients who developed early damage increase were older at APS onset (43, IQR 56 – 37 years vs. 36, IQR 50 – 26 years,  $p=0.005$ ) compared to those who did not. Gender distribution (female,  $p=0.102$ ), ethnicity (Caucasian,  $p=0.935$ ), type of APS ( $p=0.525$ ) and type of first thrombotic event (arterial,  $p=0.539$ ; venous,  $p=0.268$ ) did not differ between the groups. The final DIAPS score was significantly higher in patients with early damage increase compared to those without it (2, IQR 3 -1 vs. 1, IQR 2 – 0,  $p<0.001$ ).

In univariable analysis (**Table 4**), SAPS (OR 1.89, 95% CI 1.03 – 3.48,  $p=0.041$ ) and having a first arterial thrombotic event (OR 7.24, 95% CI 3.74 – 14.03,  $p<0.001$ ) were associated with the risk of early damage but not with the risk of early damage increase. Conversely, age at APS onset more or equal to 40 years was a risk factor for the presence of early damage increase (OR 2.81, 95% CI 1.43 – 3.19,  $p=0.003$ ), but not for the presence of early damage (OR 1.06, 95% CI 0.59 – 1.89,  $p=0.852$ ). Male gender and Caucasian ethnicity were not associated with increased odds of early damage nor early damage increase.

### Mortality

We identified 23 (11.7%) fatalities. **Table 5** show the distribution of demographic, clinical and laboratory characteristics between living and deceased patients. Patients who died were older at the time of APS onset (50, IQR 61 – 40 years vs. 38.5, IQR 50 – 27 years,  $p=0.003$ ) and had higher proportion of SAPS type (60.9% vs. 30.5%,  $p=0.004$ ) compared to those who did not die. Other demographic characteristics including gender ( $p=0.102$ ), ethnicity ( $p=0.818$ ) and

follow-up time ( $p=0.634$ ) were similarly distributed between the two groups. Regarding the type of the first clinical event, venous thrombosis (61.5% vs. 39.1%,  $p=0.041$ ), but not arterial thrombosis (42% vs. 60.9%,  $p=0.806$ ) were significantly more prevalent in the survivor group compared to non-survivor group. Serologically, only the prevalence of ACL antibody positivity differed between groups, being higher (82.6% vs. 56.3%,  $p=0.041$ ) in patients who died compared to those who did not. **Table 6** displays the predictors of mortality in our group of patients. In univariable analysis, male gender (HR 3.14, 95% CI 1.35-7.33,  $p=0.008$ ), SAPS type (HR 3.07, 95% CI 1.32-7.12,  $p=0.009$ ), age at APS onset ( $\geq 40$  years, HR 5.34, 95% CI 1.96-14.53,  $p=0.001$ ) and ACL positivity (HR 3.12, 95% CI 1.06 – 9.19,  $p=0.039$ ) were risk factors for death.

As for what accrual damage is concerned, even though median final DIAPS was significantly higher among deceased patients (2, IQR 3 – 1 vs. 1, IQR 2 – 0,  $p=0.012$ ) compared to those who survived (**Table 5**), it was not associated with the risk of death (per-unit increase HR 1.07, 95% CI 0.89 – 1.28,  $p=0.434$ ) (**Table 6**). We observed the inverse regarding the median initial DIAPS which was significantly associated with the hazard of death (per-unit increase HR 1.64, 95% CI 1.09 – 2.46,  $p=0.016$ ) (**Table 6**), but show similar median values between deceased and living patients (0, IQR 1 – 0 vs. 0, IQR 1 – 0,  $p=0.318$ ) (**Table 5**). In accordance, the presence of early damage was not associated with death (HR 1.65, 95% CI 0.73-3.78,  $p=0.231$ ). Conversely, early DIAPS increase was significantly associated with death (HR 5.40, 95% CI 2.33 – 12.52,  $p<0.001$ ) (**Table 6**), even after adjusting individually for APS category (secondary, HR 5.05, 95% CI 2.18 – 11.72,  $p<0.001$ ), gender (male, HR 5.40, 95% CI 2.29 – 12.73,  $p<0.001$ ) and age at APS onset  $\geq 40$  years (HR 3.41, 95% CI 1.43 – 8.20,

$p=0.006$ ) (**Table 6**). **Figure 1** shows Kaplan-Meier curves analysing cumulative survival between patient with and without early damage (**Fig. 1A**) and early damage increase (**Fig. 1B**).

## Discussion

In this study we explored, for the first time, the relationship between the damage acquisition kinetics as measured by DIAPS and mortality in a multi-time-point analysis of a well characterized, multi-ethnic group of APS patients followed for up to 43 years. We found that thrombotic APS patients exhibiting an increase of at least one point in damage in the first five years after illness onset have a higher mortality rate compared to thrombotic APS patients with no damage increase regardless of the type of the first thrombotic event, age at APS onset, gender, type of APS and the presence of damage at the first DIAPS assessment.

Prevention of damage is a major focal point for most physicians managing autoimmune disease patients. This is particularly true for APS as it affects young individuals and can cause severe, disabling damage from the very beginning. Neurologic involvement, mainly through strokes and transient ischaemic attacks, counts for around 30% of events in the Euro-phospholipid Project group prospective cohort study (13) and has been associated with the highest morbidity among APS patients (4,5). Thus, being able to detect those patients in greater risk of damage progression and death from the beginning is of utmost importance since no activity score is still available for APS (14). However, whether damage that arises in the firsts years of the disease as measured by the DIAPS is associated with a decreased survival has not been studied.

We found that the mortality risk did not differ whether patients had early damage or not, assessed as a binary variable (**Table 6; Fig. 1A**). We discovered, however, that the mortality was 5-times higher in those exhibiting early damage increase (at least one point) in the first five years after the disease onset (**Table**

**6; Fig. 1B).** Unlike Cervera et al (13), we report a significant decrease in the survival probability depending on the type of APS, gender and the age at onset of APS, the latter being the only affecting the risk of early damage increase as well (**Table 4**). However, the presence of early damage increase remained significantly associated with mortality risk even after individual adjustment for all these clinicodemographic characteristics (**Table 6**). In addition, while the median early DIAPS score did not differ among living and deceased patients (**Table 5**), its absolute value, as well as the DIAPS assessed at 5 years, but not from there after (DIAPS >10 years), were strong predictors of death in our population (**Table 6**). This suggests that what matters for the risk of death is the amount of damage progression in the first years of the disease rather than the total cumulative damage over the years regardless of the nature of the first thrombotic event, gender, APS type and age at disease onset.

Over the last 10 years, only a hand full of published studies have investigated factors associated with development of damage, its quantification, and correlation with mortality in patients with APS (4,5,9,12). In thrombotic APS, damage is progressive, and patients usually preserve their initial clinical features regarding the future events. Thus venous, and arterial thrombosis are usually followed by venous and arterial thrombosis, respectively (5,15). The prevalence of pulmonary emboli increased from 5.2% to almost 12% in a multi-centric cohort of 1000 APS patients followed for 10 years (13). Right before the advent of DIAPS, Dall'Ara et al (4) showed that irreversible failure of any organ progressed in a group of 30 PAPS patients. The SDI damage index increased over time, particularly in APS patients who had arterial thrombotic events in a retrospective cohort study (5). A recent long-term retrospective cohort study analysing 100

Brazilian patients (50% PAPS) over 10 years showed an increasing mean DIAPS score from 1.27 to 2.15 (12). In our study, we also used the recently validated DIAPS to assess APS damage accrual. This is an advantage over previous studies since the DIAPS was specifically design for APS. We observed the same tendency as described by previous authors, as the prevalence of accrued damage and its median score consistently increased for around 107.4% and 224.5% over the years of follow-up, respectively (**Table 2**). Although it seems not surprising, as damage is irreversible and the DIAPS can only increase, this finding echoes the notion that APS is a chronic and recurrent condition despite treatment and that damage evolves (3,15,16). It also shows that DIAPS can capture damage as it develops over time in a real-world group of patients.

Most patients with thrombotic APS have at least one point scored in DIAPS in a long-term basis. In our population, nearly 73% of patients developed damage with a median last DIAPS of 1 (IQR 2 – 0) at the end of follow-up, but prevalence higher than 90% has been reported (10,12). In contrast, only 29% of patients developed damage using SDI, with a median SDI score of 2 (IQR 3 – 1) after a median of 7.5 years of follow-up (5). SDI as a surrogate marker of damage was associated with increased mortality in a retrospective single-centre study including 135 APS patients (PAPS – 89; SAPS – 46) (5). We did not come to the same conclusion, as last DIAPS scores were not associated with the hazard of death, even though deceased patients had significantly higher DIAPS values compared to living patients at the end of the study. While it is merely speculative, we could argue that the cumulative organ involvement in APS as measured by the DIAPS is, somehow, more indolent than it is on SLE measured by the SDI. For instance, peripheral vascular domain involvement is by far more frequent

among APS (more than 60%) (10,12) than in SLE patients (around 10%) (17), in particular, vascular venous insufficiency which is responsible for nearly 42% of those events (10). Although it highly impairs quality of life (10,18), it is arguably very unlikely to influence survival. On the other hand, chronic kidney disease which affects almost 50% of SLE patients (19), and also some treatment-related damage like diabetes, affecting around 5% of SLE patients (17,20), are known risk factor for mortality in general population (21,22). These results need to be further explored in future studies.

In conclusion, an increase of at least one point in the DIAPS in the first five years after APS onset is of prognostic value. Deceased patients appear to develop damage more quickly in the first few years of illness; thus, clinicians should be willing to identify and actively minimize damage accrual, especially in the first five years of disease regardless of the nature of the first thrombotic event, gender, APS type and patient age.

## **Disclosures**

PG none to declare.

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