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4 **Diagnostic delay is associated with uveitis and inflammatory bowel disease in**  
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6 **AS: a study of extra-musculoskeletal manifestations in SpA.**  
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## Abstract

**Objectives:** To examine the prevalence of extra-musculoskeletal manifestations (EMM) and the association between diagnostic delay and their incidence in ankylosing spondylitis (AS) and psoriatic arthritis (PsA).

**Methods:** Retrospective, cohort study comprising two single centre cohorts in Europe and one multi-centre cohort in Latin America (RESPONDIA). EMMs (uveitis, inflammatory bowel disease [IBD] and psoriasis) crude prevalence was calculated across geographic area and adjusted by direct standardisation. Cox proportional hazard analysis were performed to assess the association between diagnostic delay and EMM incidence.

**Results:** Of 3553 patients, 2097 had AS and 1456 had PsA. The overall prevalence of uveitis was 22.9% (95%CI 21.1-24.8) in AS and 3.8% (95%CI 2.9-5.0) in PsA; 8.1% (95%CI 7.0-9.4) and 2.1% (1.3-2.9) respectively for IBD; 11.0% (95%CI 9.7-12.4) and 94.6% (93.0-95.9) for psoriasis; with EMM often presenting before the arthritis (uveitis 45.1% and 33.3%; IBD 37.4% and 70% in AS and PsA respectively). In the multivariable model, longer diagnostic delay ( $\geq 5$  years) associated with more uveitis (HR 4.01, 95%CI 3.23-4.07) and IBD events (HR 1.85, 95%CI 1.28-2.67) in AS. Diagnostic delay was not significantly associated with uveitis (HR 1.57, 95%CI 0.69-3.59) or IBD events (HR 1.59, 95%CI 0.39-6.37) in PsA.

**Conclusion:** EMMs are more prevalent in AS than PsA and often present before the onset of the articular disease. A longer diagnostic delay is associated with the “*de novo*” appearance of uveitis and IBD in AS, highlighting the need to enhance diagnostic strategies to shorten the time from first symptom to diagnosis in SpA.

**KEYWORDS**

Ankylosing spondylitis, psoriatic arthritis, psoriasis, uveitis, inflammatory bowel disease, diagnostic delay.

**Key Messages**

- The prevalence of uveitis and IBD is higher in AS when compared to PsA.
- Uveitis or IBD may present before the onset of the SpA diagnosis in a significant proportion of people with AS and PsA.
- A longer diagnostic delay is associated with a higher probability of uveitis and IBD in AS.

## Introduction

Axial spondyloarthritis (axSpA) encompassing ankylosing spondylitis (AS), also known as radiographic axSpA (r-axSpA), and psoriatic arthritis (PsA) are two distinct chronic inflammatory diseases under the umbrella of the spondyloarthritides (SpA).(1,2) The different SpA share common clinical and genetic characteristics including inflammation of axial (spine/sacroiliac) and peripheral joints with extra-musculoskeletal manifestations (EMMs). EMMs strongly linked to the SpA disease group are uveitis, inflammatory bowel disease (IBD) and psoriasis.(3) Their prevalence has been outlined in recent meta-analyses as higher in axSpA (pooled prevalence of uveitis, IBD and psoriasis of 23%, 6.4% and 10.2%, respectively) than PsA (pooled prevalence of 3.2% for uveitis and 3.3% IBD of 3.2%).(4, 5)

In axSpA, EMMs have been shown to impact the disease course with a recent report revealing increased cardiovascular risk that appears proportional to the number of EMMs in addition to higher axSpA disease activity and functional impairment.(6,7) By contrast, this relationship with functional disability was not seen in the OASIS cohort after 12 years of follow-up.(8) The relationship between disease duration and EMM incidence has been confirmed in several studies.(8–11) Also, HLA-B27 positivity has been shown to be associated with uveitis in several axSpA cohorts.(11,12)

Despite greater awareness and improved diagnostic techniques over the last two decades, delay to diagnosis remains a significant unmet need in SpA when compared to other chronic inflammatory arthritides. This is particularly the case in axSpA with consequent impact on disease outcome.(13) Longer diagnostic delay may also lead to higher incidence of EMMs, a hypothesis that has not been fully investigated yet. The aims of this study are to examine the prevalence of EMM and the effect of diagnostic delay in their appearance in large cohorts of AS and PsA.

## Methods

We performed a retrospective, multi-centre, cohort study across three geographic areas comprising two single centre cohorts in Europe (Chapel Allerton Hospital, Leeds, United Kingdom and Hospital Universitari de Bellvitge, Barcelona, Spain) and one multi-centre cohort in Latin America (RESPONDIA Cohort comprising Argentina, Brazil, Chile, Costa Rica, Mexico, Perú, Uruguay, Venezuela).(14) Data from patients older than 18 years with a primary clinician diagnosis of Ankylosing Spondylitis (AS) or PsA were included in the analyses. All participants provided informed written consent and the study was approved by the Hospital Universitari de Bellvitge Research Ethics Committee (Approval Number PR004/20). Individual cohort ethics and inclusion criteria details are shown in Supplementary Materials available at *Rheumatology* online. Protocol design in each cohort predated the development of ASAS and CASPAR classification criteria, hence original nomenclature utilised in the different studies referring to ankylosing spondylitis rather than r-axSpA will be utilised in this report.

Age, sex, date of onset of musculoskeletal symptoms, date of diagnosis, date of last follow-up, disease duration (calculated as time from diagnosis to last available follow-up date), HLA-B27 status, history of uveitis, inflammatory bowel disease (including Crohn's disease, ulcerative colitis and undifferentiated IBD) and psoriasis (as confirmed by a physician) together with their onset dates were collected as variables. Data from all cohorts were collected at the inclusion time point with missing values retrieved from clinical notes at a later time point.

### Statistical analysis

Demographic characteristics were compared by disease (AS and PsA) and across the three geographic cohorts. Student's t- or Mann-Whitney U- tests for continuous variables and Chi-squared for categorical variables were used as appropriate. Prevalence of EMM was calculated (with 95% Confidence Intervals (CI)) overall and for each of the three geographic areas and by disease. Crude prevalence was adjusted for age by direct standardisation using the WHO World standard population as reference.(15)

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3 Diagnostic delay was defined as the time between date of musculoskeletal symptoms onset  
4 and date of diagnosis. To examine the relationship between diagnostic delay and appearance  
5 of EMM, only EMM that occurred after the date of diagnosis were considered. Only uveitis  
6 and IBD were analysed as psoriasis predated the majority of PsA diagnoses (~85%). Only  
7 patients with available EMM onset date were included.  
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14 Diagnostic delay was categorised by the median, that is, 5 year or more delay in AS and 3  
15 years or more in PsA. An additional sub-analysis using 5 year or more in PsA was also  
16 performed. Time to-event analysis was performed and defined as time from disease diagnosis  
17 (AS or PsA) to onset of EMM or to the last available follow-up date and described using  
18 Kaplan-Meier plots and log-rank test. Cox proportional hazard analysis was performed  
19 adjusting for sex, age of onset and geographical location to assess the association between  
20 diagnostic delay on incidence of EMM. The proportional hazards assumption was examined  
21 using statistical (Schoenfeld residuals) and graphical approaches. All analysis was conducted  
22 using Stata version 16.1.  
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## 32 **Results**

### 33 *Demographic characteristics of cohort populations*

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35 Data from 3553 patients were analysed comprising 2097 with AS and 1456 with PsA.  
36 Demographic characteristics of the different cohorts are presented for AS (Table 1a) and PsA  
37 (Table 1b). Subjects with AS in Latin America were younger, with correspondingly shorter  
38 disease duration, at the time of enrolment (last available follow-up) compared to the  
39 Barcelona and Leeds Cohorts. Similar diagnostic delay was observed in the three cohorts.  
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49 For PsA, the vast majority of patients presented with PsA after psoriasis with similar  
50 proportions in all cohorts. A longer delay between psoriasis and PsA onset was seen in the  
51 Barcelona cohort, which also had longer disease duration and older age of onset when  
52 compared to the Leeds and Latin America cohorts (Table 1b). Missing data proportions of the  
53 different variables are shown in Supplementary Tables S1 and S2, available at *Rheumatology*  
54 online.  
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### *Overall prevalence of extra-musculoskeletal manifestations by geographical location and diagnosis*

The overall prevalence of uveitis in the three cohorts was 22.9% (95%CI 21.1-24.8) in AS and 3.8% (95%CI 2.9-5.0) in PsA; 8.1% (95%CI 7.0-9.4) and 2.1% (1.3-2.9) respectively for IBD, and 11.0% (95%CI 9.7-12.4) and 94.6% (93.0-95.9) respectively for psoriasis. Crude and age-standardised prevalence are presented in Figure 1 across geographical locations and disease.

### *Relationship between Extra-musculoskeletal manifestations onset and SpA diagnosis*

Divided by diagnosis, EMMs were more prevalent in the AS population (28.9%, n=600/2073 uveitis or/and IBD versus 5.8%, n=74/1284 in the PsA group). For AS patients with uveitis, the first episode of uveitis occurred before AS diagnosis in 45.1%. 33.3% of patients with uveitis reported a first episode of uveitis before the diagnosis of PsA. Regarding IBD, 37.4% of AS patients with concomitant IBD were diagnosed with IBD before the AS diagnosis and 70% of patients with PsA and concomitant IBD were diagnosed with IBD before the PsA diagnosis.

### *Diagnostic delay and extra-musculoskeletal manifestations*

For the time-to-event analysis, only EMMs that happened after the diagnosis of SpA (AS/PsA) were considered. Demographic variables and their relationship to incidence of uveitis and IBD (incidence rate ratios) after diagnosis of SpA are presented in Supplementary Table 3a and 3b, available at *Rheumatology* online. Kaplan-Meier graphs are presented for each EMM (uveitis and IBD) divided by diagnosis (AS or PsA) according to diagnostic delay (Figure 2). In the multivariable Cox model, AS patients with longer diagnostic delay ( $\geq 5$  years) had more uveitis events (hazard ratio (HR) 4.01, 95%CI 3.23-4.07) when adjusted for age of onset, sex and location. This was also observed in AS patients with IBD (HR 1.85, 95%CI 1.28-2.67). HRs for diagnostic delay were not significant for uveitis (HR 1.57, 95%CI 0.69-3.59) or IBD events (HR 1.59, 95%CI 0.39-6.37) in PsA. No differences were seen in additional analyses on PsA patients divided by a 5-year diagnostic delay cut-off (Supplementary Figure S1, available at *Rheumatology* online).



## Discussion

This study examined the prevalence of EMMs in different SpA (AS and PsA) cohorts and their relationship with diagnostic delay. Our results show that, despite some differences in demographic factors, the prevalence of uveitis and IBD is higher in AS when compared to PsA. Interestingly, when exploring the characteristics of SpA patients with EMMs, we found that a significant proportion presented with uveitis or IBD before the onset of the SpA diagnosis. Furthermore, longer diagnostic delay was associated with a higher probability of uveitis and IBD in AS, suggesting that longer time of uncontrolled inflammation might influence the incidence of EMMs.

In our study, the combined prevalence of uveitis, IBD and psoriasis in AS was 22.9%, 8.1% and 11.0%, respectively, in line with previous publications.(4) Similarly, in PsA, the combined prevalence of uveitis, IBD and psoriasis was 3.8%, 2.1% and 94.6% respectively, also consistent with results published in a recent meta-analysis.(5) There were some differences across geographic cohorts, such as higher prevalence of uveitis and IBD seen in the Leeds cohort when compared to the other cohorts in this study and a prior AS meta-analysis, which may be explained by a longer disease duration as previously shown.(4,16) Interestingly, IBD prevalence in AS was significantly lower in the Latin America population compared to the other two cohorts. This is consistent with a recent report of the multi-country observational study PROOF including axSpA patients, outlining an IBD prevalence of just 2.3% in Latin America.(17) Access to prompt secondary care or perhaps differential genetic factors underlying the populations might partly explain this difference when compared to the European cohorts.

Overall, 35% of AS and up to 70% of PsA patients in our study presented with IBD before the SpA diagnosis was made. We decided to exclude these patients in the time-to-event analysis for a number of reasons. Firstly, individuals with a pre-existing history of EMMs are more likely to experience subsequent events or flares, which may confound the results of the analysis. Secondly, longer diagnostic delay may influence the risk of subsequent episodes of flares of EMMs, and excluding patients with prior EMMs can help mitigate this potential confounding factor. Additionally, diagnostic delay was defined as the time from onset of

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3 articular (peripheral joint or spinal symptoms) to SpA diagnosis, thus including patients with  
4 pre-existing EMMs may bias the results, as EMMs may have occurred before the onset of joint  
5 symptoms. Although our decision to exclude a considerable number of patients may be  
6 viewed as a limitation, it is noteworthy that our findings align with previous literature.  
7 Specifically, a recent analysis from the Swedish Registry demonstrated that patients with IBD  
8 were diagnosed with SpA both before and after their IBD diagnosis. Notably, this association  
9 was most pronounced during the two-year period preceding and following the diagnosis of  
10 IBD.(18) Nevertheless, the cumulative incidence of SpA kept increasing in the first 10 years  
11 following the diagnosis of IBD particularly in those with Crohn's disease. In line with our  
12 findings, the strongest association in IBD was found with incident PsA (HR 12.0, CI 10.8-13.4)  
13 outlining that most PsA diagnosis happen after the IBD diagnosis. In the same manner, our  
14 data show that in approximately 40% of patients, uveitis occurred before the SpA diagnosis.  
15 These findings highlight gastroenterology and ophthalmology clinics as potential stages for  
16 earlier identification of PsA and axSpA. Indeed, awareness of the need for early referral  
17 strategies from ophthalmology to rheumatology is increasing. The SENTINEL study enrolled  
18 798 patients with anterior uveitis that were thoroughly assessed by a rheumatologist finding  
19 a prevalence of 50% for axSpA and 17.5% for peripheral SpA.(19) Referral strategies in IBD are  
20 also being explored to identify undiagnosed SpA.(20) Yet, our data show that long diagnostic  
21 delays remain an unmet need and influence the appearance of uveitis and IBD which  
22 highlights the need for multi-specialty collaborative work at the clinical level in order to  
23 improve and enhance referral strategies between ophthalmology, gastroenterology,  
24 dermatology and rheumatology.

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46 To our knowledge, this is the first study using data from cohorts across two continents to  
47 show that diagnostic delay is associated with a greater probability of uveitis and IBD in AS  
48 patients. In line with our findings, Bilge *et al* used data from a Turkish cohort including  
49 rheumatoid arthritis and SpA patients to show that delay to diagnosis was associated with  
50 uveitis in the bivariate analysis.(10) Similarly, Gevorgyan *et al* reported a longer diagnostic  
51 delay (10.9 versus 5.9 years,  $p < 0.001$ ) when comparing patients with and without uveitis in a  
52 single US academic centre.(21) These results, together with our findings, suggest that a longer  
53 delay translates into a longer period with uncontrolled inflammation which might influence  
54 the appearance of uveitis. Cakar *et al* found higher C-reactive protein (CRP) levels in AS  
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3 patients with a longer diagnostic delay, while a recent meta-analysis found higher burden of  
4 disease in those with delayed diagnosis including mobility and functional indices.(22,23)  
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6 Additionally, Varkas et al found that longer disease duration in axSpA patients was associated  
7 with a higher risk of developing anterior uveitis and IBD. Also, higher mean levels of CRP in  
8 patients with uveitis and IBD suggest a cumulative exposure to inflammation, although no  
9 data on diagnostic delay were reported.(24)  
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16 Our analysis did not find a significant association between longer diagnostic delay and EMMs  
17 in PsA. Small numbers and lower EMM incidence in PsA might be a possible explanation.  
18 However, a higher proportion of PsA patients are likely to have received disease modifying  
19 anti-rheumatic drugs (DMARDs) for peripheral joint involvement or for psoriasis treatment,  
20 which might influence the development of EMMs. Treating cutaneous psoriasis with biologic  
21 DMARDs may decrease the incidence of PsA, suggesting that a better control of inflammation  
22 may also impact the incidence of EMMs.(25) Unfortunately, treatment data were not  
23 available in our cohorts to explore this question. Larger, longitudinal studies with detailed  
24 treatment data are needed to confirm this hypothesis.  
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34 There were limitations to this study. Patients were enrolled in the study based on their  
35 primary clinician diagnosis rather than validated criteria such as the Classification Criteria for  
36 Psoriatic Arthritis (CASPAR) or modified New York (mNY) criteria.(26)(27) The characteristics  
37 of EMMs, including the time of onset, were either recalled by the participants or extracted  
38 from clinical notes, which may have introduced measurement bias. However, this limitation  
39 is common where investigators rely on patient recall or clinical notes; prospective designs  
40 also have limitations, e.g., attrition and cost. Another limitation is missing HLA-B27 data and  
41 lack of treatment data in our cohorts, both of which could potentially impact the incidence of  
42 EMMs. Moreover, CRP was not collected systematically in all cohorts, which prevented us  
43 from exploring the hypothesis that the effect of diagnostic delay on EMM events is explained  
44 by uncontrolled inflammation.  
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56 In conclusion, these data show that the prevalence of EMMs including uveitis, IBD and  
57 psoriasis is higher in AS than PsA, with a substantial proportion presenting before the onset  
58 of the articular disease. A longer diagnostic delay is associated with a greater probability of  
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3 uveitis and IBD in AS, perhaps due to uncontrolled inflammation over time. These results  
4 highlight the need for multi-specialty collaboration to improve diagnostic strategies and  
5 referral pathways in order to reduce diagnostic delay in SpA.  
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### 37 **Conflicts of interest**

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### 42 **Data availability statement**

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44 Data are available upon reasonable request, please contact the corresponding author.  
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### 47 **Supplementary data**

48  
49 Supplementary data are available online.  
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**Table 1. Demographic characteristics of AS and PsA patients from the respective geographical cohorts.**

<b>1A*</b>				
<b>AS</b>	<b>Latin America</b>	<b>Barcelona</b>	<b>Leeds</b>	<b>p-value</b>
N	1169	472	456	
Age, mean (SD), years	45.6 (14.6)	56.5 (15.8)	51.4 (14.5)	<0.001
Sex, male (%)	867 (74.2%)	335 (71.1%)	324 (72.8%)	0.44
HLA-B27 positive (%)	-	347 (77.6%)	251 (81.8%)	0.17

Age symptom onset, median (IQR), years	26.0 (19.0, 36.0)	25.0 (20.0, 33.0)	24.0 (18.0, 32.0)	<0.001
Disease duration, median (IQR), years	7.0 (4.0, 13.0)	19.5 (10.0, 35.0)	13.5 (7.0, 24.0)	<0.001
Diagnostic delay, median (IQR), years	4.0 (1.0, 10.0)	3.0 (1.0, 8.0)	5.0 (2.0, 10.0)	<0.001
<b>1B**</b>				
<b>PsA</b>	<b>Latin America</b>	<b>Barcelona</b>	<b>Leeds</b>	<b>p-value</b>
N	392	442	622	
Age, mean (SD), years	53.5 (13.6)	59.6 (14.1)	53.5 (13.2)	<0.001
Sex, male (%)	201 (51.3%)	214 (48.4%)	298 (50.6%)	0.68
HLA-B27 positive (%)	-	46 (11.8%)	57 (18.8%)	0.01
Age symptom onset, median (IQR), years	42.0 (32.0, 51.0)	41.0 (30.0, 51.0)	38.0 (27.0, 48.0)	<0.001
Disease duration, median (IQR), years	6.0 (3.0, 10.0)	13.0 (7.0, 24.0)	10.0 (6.0, 13.0)	<0.001
Diagnostic delay, median (IQR), years	1.0 (0.0, 5.0)	2.0 (1.0, 6.0)	1.0 (0.0, 2.0)	<0.001
Psoriasis duration, median (IQR), years	16.0 (9.0, 26.0)	29.0 (17.0, 40.0)	22.0 (12.0, 34.0)	<0.001
PsA diagnosed after psoriasis (%)	203 (85.7%)	366 (88.0%)	376 (87.9%)	0.65
Psoriasis-PsA delay, median (IQR), years	6.0 (1.0, 15.0)	9.0 (2.0, 19.0)	7.0 (1.0, 20.0)	0.026

\* Missing data proportion is included in Supplementary Table 1. SD: Standard Deviation, IQR: Interquartile range.

\*\* Missing data proportion is included in Supplementary Table S2. SD: Standard Deviation, IQR: Interquartile range. PsA: Psoriatic arthritis.

**Figure 1: Crude and age-adjusted prevalence of EMMs divided by location and disease.**

**Figure 2. Kaplan Meier survival curves divided by disease and EMM.**



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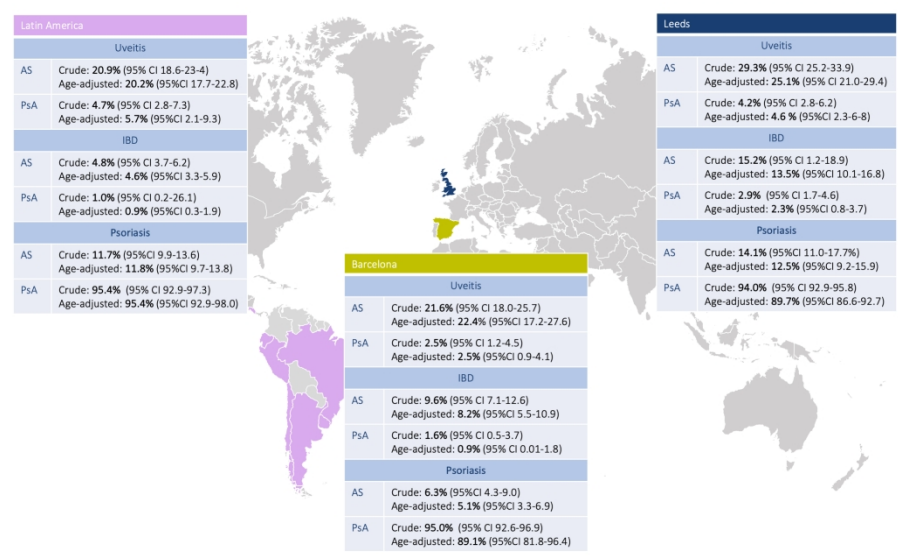


Figure 1 Crude and age-adjusted prevalence of EMMs divided by location and disease.

338x190mm (225 x 225 DPI)

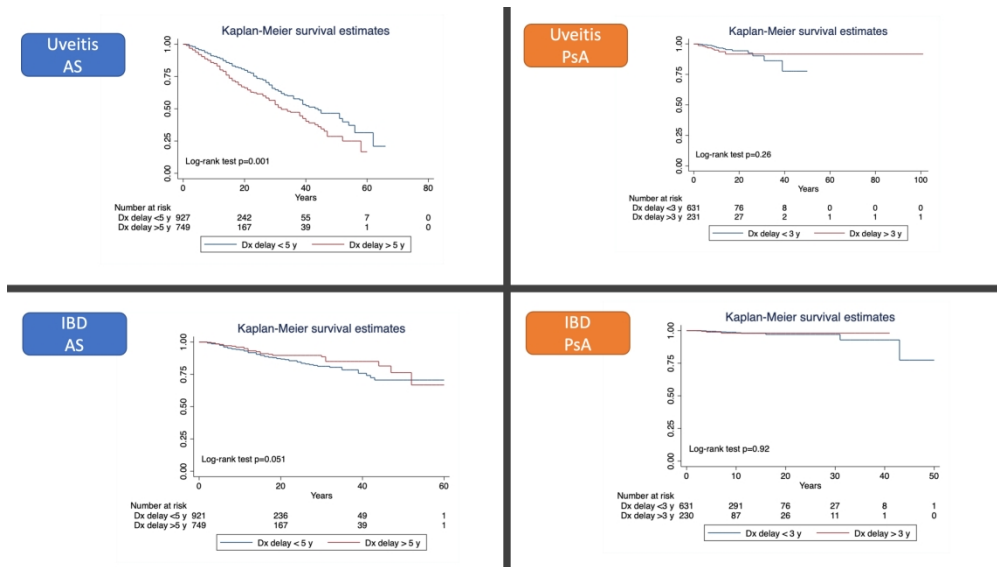


Figure 2 Kaplan Meier survival curves divided by disease and EMM.

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