MAJOR DETERMINANTS OF PROLONGED REMISSION IN SYSTEMIC LUPUS ERYTHEMATOSUS: RETROSPECTIVE STUDY OVER A 41-YEAR PERIOD

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Data are available upon reasonable request to the corresponding author.

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The authors declare no conflicting interests.

Abstract:

OBJECTIVES: To investigate predictors of sustained complete remission (CR) for 3 and 5 years, minimum.

METHODS: Retrospective observational study from january1978-december2019, including Systemic Lupus Erythematosus (SLE) patients who attended the Lupus Clinic in a tertiary hospital, for at least 3 years. We used the British Isles Lupus Assessment Group (BILAG) score and serological profile to classify patients into CR, serologically active clinically quiescent (SACQ) and serological remission (SR). Multivariable cox regression analysis was performed to investigate predictors of CR and Kaplan-Meier curves were obtained.

RESULTS: We included 564 patients, 15% achieved CR; 7% SACQ; 15% SR. 63% attained no remission. In the CR group, 73% sustained the remission for 5 or more years. Patients who did not reach any kind of sustained remission died significantly earlier ($p<0.001$). Cumulative survival figures at 5, 10, 20 and 30 years were 100, 100, 94 and 90%, respectively, for CR patients and 96, 93, 77 and 58%, respectively, for patients in the no-remission group. Significant predictors of CR were white ethnicity, adjusted hazard ratio (HR) 2.16 [95% ci 1.30-3.59] p=0.003; older age at diagnosis (>32-years), HR 1.92 [1.24-2.97] p=0.003; absence of renal involvement, HR 2.55 [1.39-4.67] p=0.002; and of antiphospholipid syndrome (APS), HR 4.92 [1.55-15.59] p=0.007.

CONCLUSION: Patients not achieving any kind of sustained remission have a higher risk of early mortality. White ethnicity, older age at diagnosis, absence of renal involvement and of APS were significantly associated with CR. Predictors for sustained CR do not change whether a 3-year or 5-year period is applied.

KEYWORDS:

Systemic lupus erythematosus; SLE; prolonged complete remission; off therapy; mortality.

KEY MESSAGES

* CR association with Caucasian, older age at diagnosis, absence of renal involvement and of APS.

* Predictors for sustained CR do not change whether a 3-year or 5-year period is considered.

* Achieving any kind of sustained remission is protective for an early mortality.

INTRODUCTION:

Systemic lupus erythematosus (SLE) is primarily a disease with relapses and remissions[1]. Disease activity is among the major determinants of organ damage, morbidity and mortality. Prolonged remissions, rather than short-lived ones, contribute to improving health outcomes in SLE patients. Prolonged remission was associated with less damage accrual[2], including lower cardiovascular risk[3].

In the treat-to-target approach in SLE, "remission" is a key target to achieve. However, various definitions have been used to define remission[4].

In previously published work[1], we defined complete remission as no SLE clinical activity (as judged by the British Isles Lupus Assessment Group (BILAG) index scores of C, D or E only) with no serological activity (normal anti-double-stranded DNA antibodies and C3 levels) for at least 3 years, with no prescription of systemic steroids or other immunosuppressive drugs (antimalarials were allowed). Using these parameters we reported that 14.5% of the patients studied achieved complete remission. Complete remission can be achieved even in patients with major organ involvement but, flares may occur even after 10 years of inactivity.

An international task force reviewing definitions of remission in SLE (DORIS) has published a consensus paper addressing the subject of complete remission and some proposals were made[5]. Although this consensus agrees that SLE remission is a durable state, it does not define how long that durability should be for. Defining the optimal definition of remission might be of great clinical value. Furthermore few studies[4,6] have investigated predictors of remission and identified differences between patients who achieved remission and those who did not.

We have now re-analysed our cohort following the DORIS consensus recommendations, both in terms of 3-year and 5-year remission, allowing us to compare our results with a broader range of studies (Supplementary table 1).

The aims of the current study were to: **(i)** identify the number of patients who achieved complete remission off therapy (minimum of 3 years) and those achieving 5-years of complete remission; **(ii)** characterize patients according to three patterns of remission: complete remission; clinical remission, the 'serologically active clinically quiescent' (SACQ); and serological remission; **(iii)** compare these data with a control group comprised of patients who did not achieve any kind of remission throughout the study; **(iv)** investigate predictors of sustained complete remission for at least 3 and 5 years, and compare both groups.

METHODS

STUDY POPULATION. Patients attending the Lupus Clinic at University College London Hospitals for a period of at least three years. All patients fulfilled at least 4 of the revised American College

of Rheumatology (ACR) classification criteria for SLE[7] and were followed up from January 1978 until December 2019. To be included in the cohort, patients had to have been attending the clinic at least once a year. At each visit, disease activity (including flare detection) was assessed using the BILAG index[8][9] and blood tests were done.

This was an observational retrospective study, with analysis of medical records collected over a period of 41 years. All data were derived from usual clinical management and patients were not asked for extra questionnaires or research procedures. No individualized or identifiable data are presented in this study. Therefore, ethical approval and informed consent were not required.

DATA COLLECTION. Individual patient records were reviewed retrospectively. The data collected included: sex, ethnicity, age at the time of SLE diagnosis, time of follow-up, duration of disease, time to achieve remission, duration of remission, development of flare, clinical manifestations of SLE during the course of the disease (mucocutaneous, musculoskeletal, cardiopulmonary, central nervous system, gastrointestinal, vasculitis, kidney or hematologic involvement), laboratory results (including anti-dsDNA antibodies, complement C3), and medications. Anti-dsDNA antibodies were considered to be positive if the patient had a value above the upper limit of normal (>50 IU) by enzyme linked immunoassay on at least 2 occasions or were positive by Crithidia luciliae.

The 'classic' BILAG was scored retrospectively from 1978-1988 from a detailed proforma completed every time the patient was assessed in the SLE clinic. Following the publication of the 'classic' BILAG paper published by Symmons DP et al[9], from 1989 to 2004, 'classic' BILAG was used and scored at each patient's outpatient visit. After BILAG 2004 was published[8], from 2005 onwards, BILAG 2004 was used and scored at each patient's appointment.

REMISSION DEFINITION AND EVALUATION. The primary goal was to capture all of those patients in complete remission for a minimum period of 3 years, and compare them with those who achieved a period of complete remission for 5 years.

We defined three levels of remission:

1. Complete remission (CR): no clinical activity (score of C, D, or E only using the 'classic' BILAG index, who were not taking steroids and immunosuppressant drugs (antimalarials were permissible) and no serological activity (dsDNA antibodies <50 IU/L, and normal serum levels of C3 complement) for a minimum of 3 consecutive years.

2. Clinical remission or 'serologically active clinically quiescent' (SACQ) disease: no clinical activity (score of C, D, or E on the BILAG index and absence of pharmacotherapy (except

antimalarials), but an active serological profile (low C3 complement level and/or high anti-dsDNA antibody levels) for at least 3 consecutive years.

3. Serological remission (SR): no serological activity (normal complement C3 and anti-dsDNA antibody levels) but with persistent clinical activity (score of A or B on the BILAG index, and/or treatment with steroids or immunosuppressive drugs) for at least 3 consecutive years.

Flare was defined as any new clinical manifestation indicating active lupus or changes to abnormal levels of anti-dsDNA antibodies and/or C3. We defined clinical flare by the development an A or B on the BILAG index (with or without a low C3 complement serum level or raised anti-dsDNA result) and serological flare by the decreased level of C3 complement and/or a high anti-dsDNA antibody result in the group of patients who have achieved only serological remission but remained clinically active. Flare definitions were used to identify patients losing remission status.

Concerning antiphospholipid syndrome (APS) presence, we only recorded as diagnosed if the case fulfilled the definition published previously by Miyakis et al.[10]

STATISTICAL ANALYSIS.

Statistical analysis was performed with IBM® SPSS® statistics version 22. After testing for normality, we compared continuous numerical variables with appropriate parametric or non-parametric tests. For categorical variables, we compared groups using Pearson's chi-squared or Fisher's exact test. Kaplan-Meier curves were used to investigate cumulative survival. Patients were censored if they were lost to follow-up or reached the end of the study. Cox regression analysis was performed to investigate several variables as possible predictors of sustained remission: sex, ethnicity, age at diagnosis, organ/system involvement (mucocutaneous, musculoskeletal, cardiopulmonary, neurological, gastrointestinal, renal and hematological) and associated/overlap conditions (APS, Sjogren's syndrome, rheumatoid arthritis and myositis). Age was investigated both as a continuous and as a categorical variable, as we used ROC curve analysis to find a cut-off. All the other variables were analysed as categorical variables. All variables with a p value < 0.05 in univariable analysis were included in the multivariable Cox regression model. Associations with a p value < 0.05 were considered statistically significant.

RESULTS

Our population was composed of 696 patients. We excluded those patients diagnosed before 1978 (n=37). We excluded the patients diagnosed after 2016 or whose follow-up at our hospital begun after 2016 (n=31). 63 patients were excluded due to irregular follow-up or insufficient data. One patient was excluded because he/she did not meet the revised ACR classification criteria for SLE[7].

We included 564 patients. Median follow-up time 12 years(Q1 7; Q3 19.5), minimum 3 years and maximum 41 years.

Table 1 shows the characteristics of the population and the comparison between the 4 groups of patients defined in the methods, based on achievement of remission for at least 3 years: 15% achieved CR for at least 3 years, 7% SACQ, 15% SR. 63% failed to achieve remission. There was no significant difference in the duration of remission in our groups.

Our cohort is multi-ethnic, with 54% white, 20% black and 12% of patients from the Indian subcontinent. Table 1 shows that in the CR group there is an overrepresentation of white patients (77%), whereas only 7% are black. ($p<0.001$).

The median age at SLE diagnosis was 27 years (interquartile range (IQR) 17 years) for the overall cohort. However, patients in the CR group were older at the time of diagnosis (32.5 (IQR 20) years) and this age difference was statistically significant when comparing with the patients who did not achieve sustained remission (median 26 years, IQR 17, $p<0.001$).

Reviewing organ/ system involvement, mucocutaneous and musculoskeletal were the most frequently involved, in each group and in the entire cohort. We found that renal involvement was less frequent in CR group (15%) comparing with each group ($p<0.001$) and general cohort (Table 1). Both neurological and haematological (haemolytic anaemia or ITP) involvement were significantly associated with the presence of APS ($p=0.012$ and 0.001, respectively).

The proportion of deaths in the group of patients that did not achieve sustained remission was significantly higher (18%) comparing with CR group (7%) and SACQ (3%), $p=0.007$. In fact, patients who did not reach any kind of sustained remission died significantly earlier ($p<0.001$), as indicated in Figure 1, which shows the patient survival Kaplan-Meier curves for each group.

The percentages for cumulative survival at 5, 10, 20 and 30 years were also determined. Cumulative survival figures at 5, 10, 20 and 30 years were 100, 100, 94 and 90%, respectively, for patients who achieved CR and 96, 93, 77 and 58%, respectively, for patients in the no-remission group.

Table 2 shows the causes of death for the several groups of patients. As reported previously, most deaths occurred among the patients who did not achieve sustained remission (55 out of 65 deaths), and the main causes were infection (31% overall), cancer (22%) and cardiovascular (14%).

We have also analysed a subgroup of patients who achieved a more prolonged sustained remission - at least 5 years. Of the 564 patients, we found that only 63 (11%) achieved sustained CR 5 years. In this group, only 8 (13%) patients had a relapse after 5 years of remission. In Table 3, we compared these patients with those with sustained remission for a shorter period (3 or 4 years), and no

statistically significant differences were found (although for some variables the number of patients may be too low to have statistical power).

Table 4 shows the adjusted hazard ratios for the significant predictors of complete remission for at least 3 years or 5 years. The variables that are significantly associated with achieving complete remission are the same in both groups, with only small differences in the hazard ratios. Significant predictors of CR were white ethnicity, adjusted hazard ratio (HR) 2.16 [95% CI 1.30-3.59] p=0.003; older age at diagnosis (>32-years, supplementary figures 2 and 3), HR 1.92 [1.24-2.97] p=0.003; absence of renal involvement, HR 2.55 [1.39-4.67] p=0.002; and no concomitant antiphospholipid syndrome (APS), HR 4.92 [1.55-15.59] p=0.007. Figure 2 shows the Kaplan-Meier curves illustrating these results.

DISCUSSION

Remission is an important target in the management of SLE patients[5], because there is a relationship between poor control of disease activity and the degree of organ damage[11]. Notably, since the first definition of disease remission in 1956 by *Dubois*[12], a unified definition for this term is still lacking: several different definitions have been proposed (Supplementary table 1). Recently, the international study group (DORIS) proposed criteria for defining remission which are testable[5].

We have taken a somewhat different approach to that of the DORIS group by distinguishing three kinds of remission. We have previously used[1] these 3 categories CR, SACQ and SR, and we wished to be consistent in our approach. The original concept of SACQ was that of Gladman et al[13]. In our own study[14], we showed that the majority of patients in this category did flare within five years, thus for us it remains a small but important group to distinguish as it offers a warning to the clinician that these patients are at greater danger of flaring than those who are both clinically and serologically quiescent.

Equally important, we recognise that some patients are clearly active clinically although 'serologically in remission' – our SR group. We identified this situation in twice as many patients as those in the SACQ group and the same as those achieving CR. Clearly these patients must be treated appropriately even if their anti ds DNA antibody and C3 levels may be normal.

In this study, we have extended our original study[1] with 32 additional patients and the cohort was followed for longer (9 years more) and we show that the 5 year CR rate is little different form the 3 year period (see discussion below). Importantly, we have shown that CR is associated with much improved survival (for up to 30 years follow up) and have identified some important factors linked

to survival notably in this group: white ethnicity (p=0.003), older age at diagnosis (p=0.003), absence of renal involvement (p=0.002) and no concomitant APS (p=0.007).

In our study, 11% (63/564) achieved CR lasting at least 5 years. Similar results were described by *Tsang-A-Sjoe et. Al* [6], who reviewed 183 patients with a median follow-up duration of 5 years, 12.8% (15/117) achieved the CR (SLEDAI-2K=0, antimalarials were the only drugs allowed). Using the same definition as Tsang-A-Sjoe[6], *Zen et al.*[11] found 9.2% (27/293) patients in CR. The Naples and Rome Lupus Clinics[3] found slightly more patients in CR in their cohort (14.6% (43/294)). It is notable that our group of patients in CR for at least 5 years is larger than other groups who, using a similar definition for CR, reported: 0,8% (1/115), 2,4% (38/1613), 6,9% (12/173), 7.1% (16/224) respectively for the Pisa[15], Toronto[16], Cruces-Bordeaux[17] and Padua[2] cohorts.

Similar to previous studies in the UK[1], Toronto[16], China[18] and Netherlands[6], we have found that older age at diagnosis is associated with sustained CR. This may be related to the fact that older patients tend to have less aggressive disease. No statistical significance was found with respect to gender and CR. However, we found a significant proportion of caucasian patients in the CR group. *Steiman et al*[16] found that, in their CR group, 82.4% were white, 5.3% Asian but no black patients were studied in this group.

We have also found that a lack of renal involvement is associated with sustained CR, as has been noted previously[2,6,18]. In contrast, the Padua caucasian cohort[2], 87.5% had arthritis and 18.8% haematological involvement, but surprisingly only 37.5% had cutaneous involvement in the analysis of cumulative disease manifestations.

Interestingly we report an absence of antiphospholipid syndrome (APS) is linked to sustained complete remission; which are unaware of having been reported previously. Zen et al[11] found that APS is associated with damage.

Because of the difficulties in achieving complete remission, Franklyn *et al.* defined Lupus Low Disease Activity State (LLDAS), and demonstrated that patients who achieved this activity state, have less organ damage[19]. Sharma *et al.* reported a similar finding, and concluded that achieving LLDAS 50% of the time (LLDAS-50) is associated with a reduction of severe damage and mortality[20]. In our study, we used three definitions: CR, SACQ and SR. It is important to mention that most of the previous papers used the SLEDAI score to evaluate disease activity[6,11,15–18,21–23], but we used the BILAG activity index which has shown a correlation with other methods including SLEDAI[24]. Tselios et al[4], in an inception cohort analysis, defined CR for at least 10 years, found 10,1% in CR and 18% in LDA (Low Disease Activity) in their 267 patients. They concluded that long-term LDA might be a reasonable outcome for clinical and therapeutic practice. In our study we have two groups of patients who have low disease activity, but do not meet the CR definition: SACQ (7%)

and SR (15%). The duration of remission was longer in the CR group than in the SACQ group, in terms of survival, both groups (SACQ and SR) have a statistically significant difference comparing with the no remission group (Figure 1).

As we mentioned previously, there is no consensus about the time to define CR; some authors used 3 years[1], others 10 years[4], but mostly authors used 5 years[2,3,6,11,15–18,21–23]. One of aims of our study was to compare patients in CR for 3 years and patients in CR for 5 years or more, to try and identify the predictors for a long-term CR. This is the first study which compare this groups (Table 3). Zen et al[11], compared 1, 2, 3, 4 and 5 years in remission and concluded that remission during two consecutive years protects against damage, we noted that analysing the adjusted hazard ratio, some variables are associated with long term CR thus white ethnicity, older age at diagnosis, absence of renal involvement and no concomitant APS (Table 4).

Our cohort has been followed for up to 41 years, with a median follow-up of 12 years (maximum 41 years). This study has the longest follow-up time of which we are aware and a large number of patients were followed up (n=564). During the follow-up, our patients were encouraged to contact us if they felt they were flaring, which we think, though cannot be completely certain, would minimize any flares we might have missed. In the 3 and 4 years CR group, we have found 11 patients (48%) which were lost to follow-up, while, in the ≥5 years CR group, there were 29 patients (46%) that were lost to follow-up (Supplementary figure 1).

We recognize as limitations of this study: its retrospective and unicentric nature, the fact that we did not collect the cumulative glucocorticoid dose before the achievement of remission, or record in detail factors which might have contributed to adverse outcome e.g. smoking, sustained increased cholesterol levels, family history of cardiovascular disease. We also recognise that our survival analysis might be biased by the fact that a significant proportion of patients were lost to follow-up after 3 years in remission. Also, C4 level was not available during the follow-up and therefore the authors cannot exclude that patients classified in serological remission might have had C4 hypocomplemetaemia.

It was beyond the scope of this study to compare our data with the DORIS consensus definition for remission on therapy[5]. However, we are planning to do that in a future analysis.

Our findings, supported in part by the work others[2,16,22] did, allows rheumatologists looking after patients with SLE to be confident that a full and sustained remission and good long-term survival (90% at 30 years in our cohort) can be achieved. Currently however, the former is only evident in about one patient in six. As is widely recognised, renal disease and, in our experience co-existent anti-phospholipid antibody syndrome, are both associated with a worse outcome. Caucasian patients too seem to fare better long term.

CONCLUSION

In conclusion, patients not achieving any kind of sustained remission have a higher risk of early mortality. White ethnicity, older age at diagnosis, absence of renal involvement and of APS were significantly associated with CR. Predictors for sustained CR do not change whether a 3-year or 5-year period is applied.

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Table 1: Comparison between patients with different levels of sustained remission (≥3 years) and no remission.

	Total	Complete remission 3y	Clinical remission 3y (SACQ)	Serological remission 3y	No remission	P
Total, N (%)	564 (100)	86 (15)	38 (7)	85 (15)	355 (63)	
Females, N (%)	520 (92)	78 (91)	36 (95)	79 (93)	327 (92)	0.878
Ethnicity						
White, N (%)	305 (54)	66 (77)	26 (68)	36 (42)	177 (50)	
Black, N (%)	112 (20)	6 (7)	7 (18)	17 (20)	82 (23)	
Subcontinent, N (%)	68 (12)	10 (12)	2 (5)	17 (20)	39 (11)	<0.001
Asian, N (%)	32 (6)	2 (2)	1 (3)	6 (6)	24 (7)	
Other, N (%)	47 (8)	2 (2)	2 (5)	10 (12)	33 (9)	
Age SLE diagnosis(y), median (IQR)	27 (17)	32.5 (20)	30 (19)	27 (16)	26 (17)	<0.001
Time follow-up since SLE diagnosis(y), median (IQR)	14.5 (13)	21 (18)	22.5 (17)	17 (18)	13 (11)	<0.001
Duration of remission(y), median (IQR)	7 (8)	9 (10)	7.5 (5)	6 (6)	N/A	0.121
Organ/system involvement						
Mucocutaneous, N (%)	496 (88)	80 (93)	34 (90)	80 (94)	302 (85)	0.046
Musculoskeletal, N (%)	519 (92)	83 (97)	36 (95)	78 (92)	322 (91)	0.309
Renal, N (%)	200 (36)	13 (15)	8 (21)	36 (42)	143 (40)	<0.001
Serositis or cardiopulmonary, N (%)	222 (39)	25 (29)	13 (34)	33 (39)	151 (43)	0.125
Neurological, N (%)	94 (17)	10 (12)	3 (8)	23 (27)	58 (16)	0.016
Haemolytic anaemia or ITP, N (%)	53 (10)	8 (9)	3 (8)	7 (8)	35 (10)	0.945
Gastrointestinal, N (%)	11 (2)	0	1 (3)	3 (4)	7 (2)	0.405
Associated conditions/overlap						
Antiphospholipid Syndrome, N (%)	56 (10)	3 (4)	7 (18)	11 (13)	35 (10)	0.048
Sjogren's syndrome, N (%)	76 (14)	15 (17)	8 (21)	15 (18)	38 (11)	0.084
Myositis	19 (3)	1 (1)	3 (8)	3 (4)	12 (3)	0.298
Rheumatoid arthritis	26 (5)	2 (2)	0	9 (11)	15 (4)	0.020
Deaths, N (%)	65 (14)	4 (7)	1 (3)	5 (7)	55 (18)	0.007

SLE: Systemic Lupus Erythematosus; y: years; IQR: interquartile range; ITP: immune thrombocytopenia. The p value refers to the comparison between the 4 groups (except in duration of remission - only 3 groups).

Table 2: Causes of death for the different groups of patients

Cause of death	Complete remission 3y	Clinical remission 3y (SACQ)	Serological remission 3y	No remission	Total
Infection, N (%)	1 (25)	0 (0)	0 (0)	19 (35)	**20 (31)**
Cancer, N (%)	3 (75)	0 (0)	2 (40)	9 (16)	**14 (22)**
Cardiovascular, N (%)	0 (0)	0 (0)	2 (40)	7 (13)	**9 (14)**
Disease activity, N (%)	0 (0)	0 (0)	0 (0)	5 (9)	**5 (8)**
Other, N (%)	0 (0)	0 (0)	1 (20)	9 (16)	**10 (15)**
Uncertain, N (%)	0 (0)	1 (100)	0 (0)	6 (11)	**7 (11)**
Total, N (%)	**4 (100)**	**1 (100)**	**5 (100)**	**55 (100)**	**65 (100)**

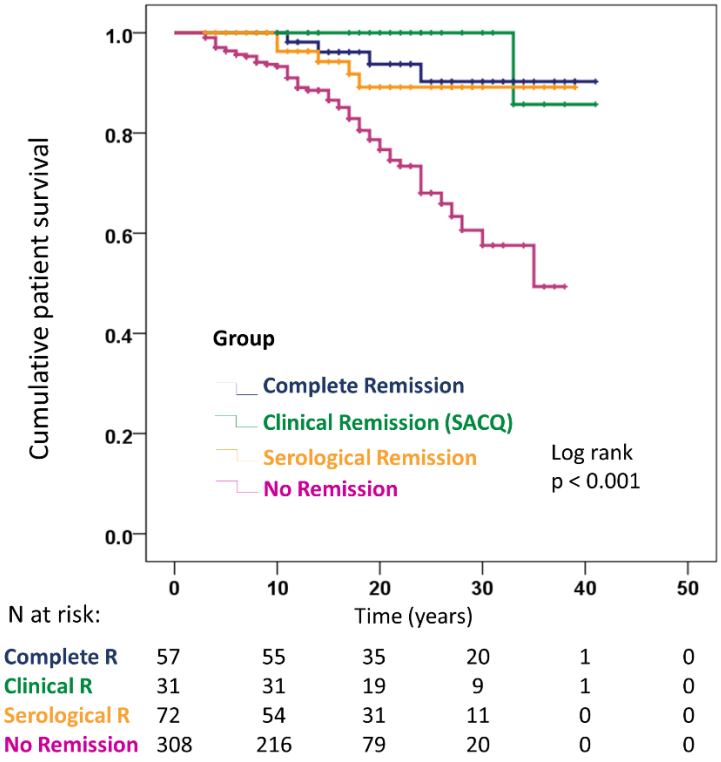
Table 3: Comparison – Comparison between patients who achieved sustained complete remission for at least 5 years and patients who achieved sustained complete remission for 3 to 4 years. Cause of death in group 3-4 was cancer; in group ⩾ 5 causes were infection and cancer.

	Complete remission 3-4y	Complete remission ≥ 5y	P
Total, N (%)	23 (27)	63 (73)	
Females, N (%)	23 (100)	55 (87)	0.102
Ethnicity			
White, N (%)	17 (74)	49 (78)	
Black, N (%)	3 (13)	3 (5)	
Subcontinent, N (%)	2 (9)	8 (13)	0.524
Asian, N (%)	0 (0)	2 (3)	
Other, N (%)	1 (4)	1 (2)	
Age SLE diagnosis(y), mean ± SD	29 ± 13	35 ± 14	0.076
Time follow-up since SLE diagnosis, mean ± SD	18 ± 9	23 ± 10	0.018
Organ/system involvement			
Mucocutaneous, N (%)	22 (96)	58 (92)	1.000
Musculoskeletal, N (%)	22 (96)	61 (97)	1.000
Renal, N (%)	3 (13)	10 (16)	1.000
Serositis or cardiopulmonary, N (%)	6 (26)	19 (30)	0.713
Neurological, N (%)	4 (17)	6 (10)	0.447
Haemolytic anaemia or ITP, N (%)	3 (13)	5 (8)	0.436
Gastrointestinal, N (%)	0 (0)	0 (0)	-
Associated conditions/overlap			
Antiphospholipid Syndrome, N (%)	2 (9)	1 (2)	0.173
Sjogren's syndrome, N (%)	4 (17)	11 (18)	1.000
Myositis	1 (4)	0 (0)	0.267
Rheumatoid arthritis	0 (0)	2 (3)	1.000
Deaths, N (%)	2 (12)	2 (5)	0.575

SLE: Systemic Lupus Erythematosus; y: years; IQR: interquartile range; ITP: immune thrombocytopenia. The p value refers to the comparison between the 2 groups (Chi-squared/Fisher's exact test or Student's T test).

Table 4: Adjusted hazard ratios for predictors of sustained complete remission, by multivariable COX regression analysis.

Predictors of remission ≥ 3y	B coefficient	HR [95%CI]	p
White ethnicity	0.768	2.155 [1.295-3.586]	0.003
Age diagnosis SLE > 32	0.652	1.920 [1.242-2.968]	0.003
No renal involvement	0.935	2.548 [1.391-4.665]	0.002
No antiphospholipid syndrome	1.592	4.915 [1.549-15.594]	0.007
Predictors of remission ≥ 5y	**B coefficient**	**HR [95%CI]**	**p**
White ethnicity	0.822	2.275 [1.244-4.163]	0.008
Age diagnosis SLE > 32	0.892	2.439 [1.459-4.076]	0.001
No renal involvement	0.806	2.339 [1.116-4.493]	0.023
No antiphospholipid syndrome	2.397	10.994 [1.521-79.451]	0.018



N at risk:

Complete R	57	55	35	20	1	0
Clinical R	31	31	19	9	1	0
Serological R	72	54	31	11	0	0
No Remission	308	216	79	20	0	0

Figure 1: Cumulative patient survival - Kaplan-Meier curves showing cumulative patient survival in patients who reached different levels of sustained remission (for at least 3 years).

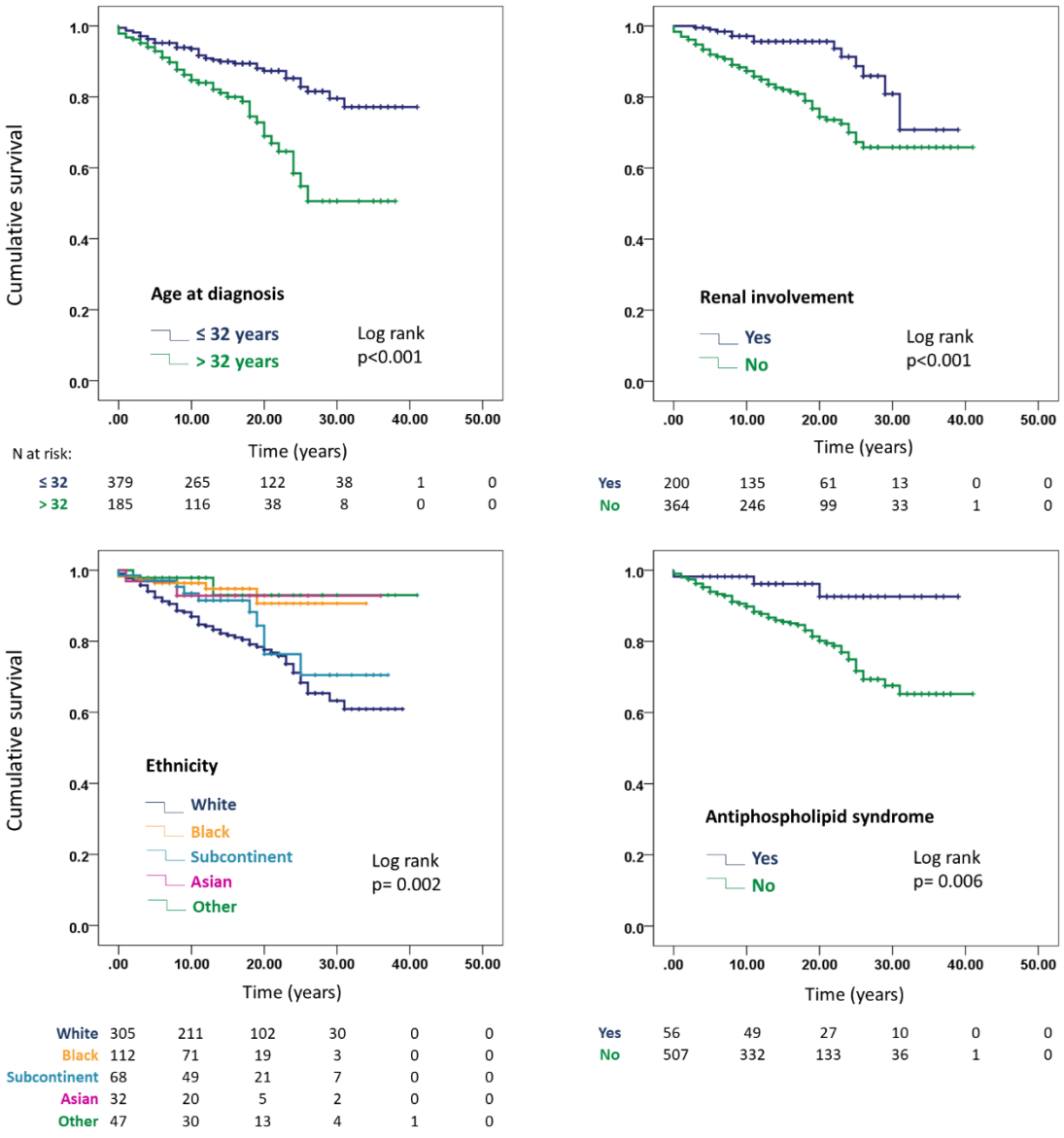


Figure 2: Cumulative survival free of complete remission - Kaplan-Meier curves showing cumulative survival free of complete sustained remission (at least 3 years), in different groups of patients, after the diagnosis of SLE. We report time to achieve complete remission. As the curves go down, more patients are achieving complete remission.