

**Title: Analysis of trends and causes of death in SLE patients over a 40-years period in a cohort of patients in the United Kingdom**

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## **ABSTRACT:**

**Background:** Systemic Lupus Erythematosus (SLE) an autoimmune rheumatic disease with a complex pathogenesis, remains potentially life-threatening. SLE patients have increased morbidity and premature mortality compared to non-SLE patients. The five-year survival rate has improved from < 50% in the 1950s to > 90% in the 1980s. Lupus patients still have a mortality risk three times that of the general population.

**Objectives:** To provide a detailed analysis of the causes of death, main characteristics and trends in the management of the deceased SLE patients from the lupus clinic at the University College London Hospital (UCLH); during the past four decades.

**Methods:** This was a non-interventional, retrospective study based on historical real-world data from paper and electronic records of patients followed up at UCLH. The analysis focused on data collected between 1st January 1978 and 31st December 2018. We collected the : causes of death, duration of disease, key laboratory and clinical parameters and the treatment received. We compared the results from the four decades to ascertain trends in the causes of mortality.

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS), version 22.0. The 95% confidence intervals for the means of data were calculated.

**Results:** 111 SLE patients (15%), died during follow-up. . Their median age was 51 years (interquartile range (IQR) = 38-63 years) and the median duration of disease, 15 years (IQR = 8.5-24 years). The main causes of death in the past 40 years were infection (31.7%), cancer (26.7%) and cardiovascular disease (CVD) (21.8%).

93.6% of these patients were immunosuppressed. During the 40-year period, there were several therapeutic developments notably the introduction of mycophenolate mofetil (MMF) and rituximab; the latter initially only given to patients when more conventional immunosuppressants had failed, but more recently offered to patients at diagnosis. There was a statistically significant increase in the use of hydroxychloroquine (HCQ), MMF and rituximab. In contrast, the use of Azathioprine (AZA) and steroids, hardly changed over time.

**Conclusions:** This retrospective review shows how epidemiological factors, causes of death and treatment of SLE patients have changed during the last 40 years in the UCLH cohort.

## **INTRODUCTION:**

Systemic Lupus Erythematosus (SLE) is an autoimmune rheumatic disease with a complex pathogenesis, causing diverse symptoms and signs. Patients with SLE have increased morbidity and premature mortality compared to non-SLE patients [1]. Recent studies found that five- and ten-year

survival rates for patients with SLE improved from less than 50% in the 1950s to more than 90% in the 1980s [2].

While mortality is decreasing for the population at large, the excess mortality attributable to SLE has remained excessive. The overall mortality is two to three times compared with non-SLE patients [3]. A bimodal distribution of the causes of death was reported in studies (in North America and Europe) [4, 5]: early mortality is more frequently attributed to active disease or infection, and late mortality is more often due to cardiovascular disease (CVD).

In this study, the causes and trends of mortality over a 40-year period in SLE patients at University College London Hospital (UCLH), United Kingdom (UK); a major SLE referral center; were investigated. Epidemiological data, duration of disease, clinical manifestations of the patients and drugs prescribed in each decade were also evaluated.

### **MATERIAL AND METHODS:**

This was a non-interventional, retrospective study based on historical real-world data from the paper and electronic records of patients followed up by Rheumatology department of the UCH. The analysis focused on data collected between 1st January 1978 and 31st December 2018. We collected the following data: causes of death, duration of disease, key laboratory and clinical parameters and the treatment received during the course of disease; over the different decades. We were interested to compare the results from the four decades to determine if there were any changing trends in the causes of mortality in our cohort. For patients who moved away or ceased to attend our own unit, we were able to obtain information from them directly, or their general practitioners or other rheumatologists who had taken over their care so that we lacked long term follow up data on <5% in all.

Among the laboratory parameters, we collected the following data: positivity or negativity of rheumatoid factor (RF) or anti-dsDNA (defined as Crithidia positive or a dsDNA enzyme linked immunosorbent assay (ELISA) assay twice the upper limit of normal on two occasions or more), complement C3 (C3) levels (by laser nephelometry), the presence (detected by commercial ELISA) of anti-Sm, anti-ribonucleoprotein (anti-RNP), anti-Ro and anti-La antibodies. Likewise, we reviewed the presence of leukopenia and lymphopenia, hemolytic anemia or thrombopenia in patients who died during this period.

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS), version 22.0. Data was presented as median and interquartile range (IQR). The 95% confidence intervals for the means of data were calculated. For categorical variables, the values were presented as frequencies with corresponding percentages and statistical test to determine if there is a significant relationship between qualitative or categorical variables in almost all cases using the Chi-square test. For the comparison of the numerical variables a non-parametric test, Kruskal-Wallis, was applied.

### **RESULTS:**

#### Demographic characteristics

Over this 40-year period analyzed, a total of 725 SLE patients have been followed up at the UCLH SLE clinic. A total of 111 patients (15%) from this SLE cohort, died during the follow-up from 1978 to 2018. Of these patients, 11 (10%) died from 1978-1997, 20 (18.3%) from 1988-1997, 40 (36.7%) from 1998-2007 and in the last decade, from 2008-2018, 39 (35%) patients died.

102 patients (92%) were female. The median age of the patients was 51 years (IQR 38-63 years). The global median duration of disease in those who died was 15 years (IQR 8.5-24 years), but it improved from 3 years (IQR 0.5-10 years) during the first decade to 18.5 years (IQR 2-44 years) in the second ( $p < 0.0005$ ), 13.5 years (IQR 1-35 years) in the third ( $p = 0.006$ ) and 20.5 years (IQR 0.5-44 years) in the last decade ( $p < 0.0005$ ).

Patients who died during the first decade (1978-1987), were younger than those who died during the most recent decade (2008-2018), ( $p = 0.002$ ). The median age was 35 years (IQR 16-59 years) in 1978-1987 and 56 years (IQR 22-90) in the last decade (2008-2018).

With respect to ethnicity, most patients who died, 72 (65.5%), were Caucasian. 23 cases (21%) were Afro-Caribbean. 14 patients (12.5%) were South Asian and 1 patient (1%), East Asian. Reviewing each decade, we observed this same trend with a slight variation in the final decade: 24 (63.2%) cases were Caucasian. 8 (21%) from South Asia, and 5 (13.2%) patients were Afro-Caribbean.

The main causes of death in the past 40 years were infections (31.7%), followed by cancer (26.7%) and cardiovascular disease (CVD) 21.8%; 19.8% was due to other causes (including suicide, liver failure and road traffic accident). From 1988-1997, the majority (8 (47%)) of SLE patients died from a cardiovascular condition. However, in the last two decades, infections were the cause of most deaths in SLE patients: 13 (32.5%) from 1998-2007 and 12 (36.5%) from 2008-2018. These differences were not statistically significant.

#### Laboratory parameters.

Among the laboratory data of the deceased patients in the 40 years of this study, of the 111 patients, 71 (65%) had raised anti-dsDNA antibodies ; 51 (52%) had reduced C3 levels and 35 (31.5%) patients had a positive RF, 13 (12%) anti-Sm, 27 (24.3%) anti-RNP, 35 (31.5%) anti-Ro and 14 (12.5%) anti-La antibodies. Of the antiphospholipid antibodies tested, 21 (19%) had lupus anticoagulant (LA) and 32 (29%) anticardiolipin antibodies (aCL): 15 (14.5%) IgG, 8 (7%) IgM and 9 (8%) G and M. Most of these results are similar to those described in other cohorts [6, 7]. Finally, 47 (42%) had leukopenia and 88 (80%) had lymphopenia. Thrombopenia was recorded in 24 patients (21.5%) and hemolytic anemia in 11 (10%).

For most parameters, none of the variations in laboratory results during the four decades, was statistically significant. However, comparing the first and the last 20 years, we found that C3 levels were lower in more patients during the last 20 years ( $p = 0.034$ ).

#### Lupus Nephritis and Central Nervous System involvement.

The presence of lupus nephritis (LN) or central nervous system (CNS) involvement, are adverse factors associated with a poorer prognosis in SLE [8, 9, 10]. In our group of deceased patients, 44 (40%) were diagnosed with LN and 29 (26.4%) had one/more manifestation of CNS involvement. We did not find differences when we compared the four decades, but when we compared the percentage of patients in the first 20 years of analysis with the next 20 years, an increased number of patients with LN from 25.8% to 46.2% in the last 20 years ( $p = 0.05$ ) was noted. Analysing the histological type of LN for patients with LN, by World Health Organization (WHO) class [11], most patients (53%) were class IV LN, 29.4% class III and 11.8% class V. 6% were classified as class IV/V.

#### Treatment.

93.6% of patients were immunosuppressed using azathioprine (AZA), cyclophosphamide, cyclosporine, methotrexate (MTX), mycophenolate mofetil (MMF), rituximab and/or corticosteroids;

as recommended by the European League Against Rheumatism (EULAR) for the management of SLE [12]. Most patients had received corticosteroids of doses  $\geq 20$  mg of prednisone daily (91%) at some point. 8% received lower doses,  $< 20$  mg.

From 1978 to 1988, most patients received AZA (7, 63.5%); and it was also the main immunosuppressant (IS) treatment in the next decade (15, 79%). In the following decades, there was a notable increase in the use of other IS drugs notably MMF. MMF was originally approved by the Federal Drug Administration (FDA) in 1995 for prevention of renal transplant rejection and it was subsequently used in lupus nephritis initially in uncontrolled cohort studies, which were then followed by randomized controlled trials [13]. Thus, from 1978 to 1997, no patient who died received MMF; received from 1998 to 2007, 9 patients (22.5%) treatment with MMF and 8 (21%), from 2008 to 2018.[14, 15, 16].

In spite of the differences and changes in drugs prescribed over 40 years, the number of patients receiving some drugs in each decade was too small to apply a statistical test. Assessing the use of AZA and hydroxychloroquine (HCQ) we noted an increased use of HCQ over time, that was statistically significant ( $p = 0.05$ , by chi square).

When we compared the periods, 1978-1997 and 1998-2018, the main changes in treatment were the increasing use of MMF: none during first two decades to 17 (22.8%) in the second 20 years ( $p = 0.003$ ). We also noted a progressive increase in the use of Rituximab: no patient from 1978 to 1997; to 14 (18%) from 1998 to 2018 ( $p = 0.01$ ). We also observed an increasing use of Methotrexate (MTX): from 1 patient (3.3%) in the first two decades to 8 (10.3%) on the second 20-year period, ( $p = 0.44$ ). In contrast, the use of AZA and steroids, hardly changed over the decades. With respect to AZA, 22 patients (73.3%) received it during the first 20 years, and 57 (73.1%) during the last 20; ( $p = 1.0$ ). Steroids up to  $\geq 20$  mg, were prescribed in 28 patients (90.3%) from 1978 to 1997 and in 72 (92%) from 1998 to 2018 ( $p = 0.712$ )

## **DISCUSSION:**

The major findings in this retrospective review of a large number of SLE patients followed up carefully over 40 years showed that patients who died during the first decade (1978-1987), were younger than those who died during the most recent decade (2008-2018), ( $p = 0.002$ ); and there was an increase on the median age at death from 35 years (IQR 16-59 years) to 56 years (IQR 22-90), respectively. Another important finding was that the median duration of disease (from diagnosis to death) improved over the decades, from 3 years (IQR 0.5-10 years) during the first decade to 20.5 years (IQR 0.5-44 years) in the last one ( $p < 0.0005$ ).

With respect to treatment, in this cohort we observed a significant increase in the use of HCQ ( $p = 0.05$ ) but no significant change in the use of AZA: from 1978 to 1987 (7, 63.5%); and it was also the main immunosuppressive drug in the next decades being used in 15 patients (79%) from 1988 to 1997, 34 (85%) from 1998 to 2007 and 23 (60%) from 2008 to 2018. We began using rituximab in our unit in 2000 and thus its increased use was evident comparing the first and last 20 years: the first 20 years no patient were treated with it and since 2000, 14 (18%) of the SLE patients who died had received rituximab ( $p = 0.01$ ). Current therapeutic approaches involve immunomodulation and immunosuppression and are targeted to the specific organ manifestation [17], and this, trend toward more intense immunosuppressive treatment to obtain better control of the disease, especially its renal manifestations [18, 19] was noted.

We noted an increase in the number of patients dying who were known to have LN from 25.8% the first 20 years to 46.2% in the last 20.

In this report, we also identified the causes of death in our SLE cohort. The commonest cause of death were infections (31.7%) as reported in other studies [20, 21, 22] and cancer (26.7%). But over the decades, with the past of years, there were some changes. Interestingly from 1988 to 1997, 47% of SLE patients died from a cardiovascular condition but in the last two decades, infections were the main cause of death. Clearly greater use of immunosuppressants for controlling disease, especially renal disease, does predispose to infection [23, 24, 25]. It is also known that SLE patients have an increased risk of CVD and myocardial infarction [26, 27] and perhaps the primary prevention of CVD and the use of new immunosuppressive drugs could explain these changes on the main causes of death over the decades.

This study shows how epidemiological factors, causes of death and treatment of SLE patients have changed during the last 40 years among those followed up at UCLH. It is notable that just only one new biologic drug (belimumab) has been approved by the Federal Drug Administration for SLE [28, 29]; though NHS England does permit the use of rituximab in the treatment of SLE. Rituximab has also been recommended in the guidelines issued by the American College of Rheumatology [30] and the European League against Rheumatism (EULAR) [2]. However, persistent mortality gap in SLE compared to those without, may be related to the lack of major breakthroughs in SLE care; in stark contrast to the advances observed with the introduction of several successful biologic approaches in patients with rheumatoid and psoriatic arthritis [31, 32].

We noted that causes of death have changed little over the 40 years, with infections remaining very prominent. We suggest standardized protocols for vaccinations, and the more judicious use of steroids and immunosuppressives are needed to help minimise infections are needed. The persistence of cardiovascular events, highlights the importance of being vigilant about discouraging smoking, normalising blood lipids and and maintaining a normal blood pressure.

Finally, screening cancer protocols for detecting cancer at an earlier stage because of the slightly increased higher risk of some cancer in SLE patients [33, 34, 35], could help to improve survival rate.

The limitations of this study are that it represents results from a single centre and some patients could not be traced to determine their long term outcome. However, this latter number represented <5% of our patients overall. It is possible that being a Centre with an established interest in SLE lead to our being referred a larger number of patients with more aggressive disease. Nevertheless, we believe that the dedication of our staff over a long period of time, looking after over 700 patients, with the unitary ethos that a single centre approach offers, does enable us to present data likely to be more widely representative of what has happened to SLE patients elsewhere.

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