Title of the study

“Survival analysis of a Lupus cohort”

Place of study

Department of Clinical Immunology and Rheumatology

Christian Medical College

Vellore, Tamil Nadu,

India
Department of Clinical immunology and Rheumatology: 

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Degree and Subject: DM, Rheumatology: 

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**Background:** 

Systemic Lupus Erythematosus is one of the common illnesses in a Rheumatology department. It affects mostly women in the reproductive age group. Few decades back it was a disease with high mortality. There has been an increasing understanding on the etio-pathogenesis of this disease. Improved investigations and treatment modalities have improved the survival of these patients significantly. Most of this data is from developed countries. In view of the difference in background health of the population, differences in availability of health care, and genetic differences the survival needs to defined for an Indian population in an Indian setting. This study attempts to do this, particularly because the information from India regarding his is limited. 

**Methods:** 

A cohort of 225 patients admitted in CMC from 2007 to 2010 were assessed for their duration of survival since diagnosis. This group of patients had their various parameters documented during the admission in their history,
examination, investigations and treatment. This was retrieved onto an excel sheet from the clinical work station. These patients were followed up during their review visits in the outpatient or inpatient setting as the case may be. A Kaplan Meir survival curve was made for these patients. Their significance of correlation with any of the clinical or laboratory indices were evaluated by log rank test. The same group of patients was also assessed for evidence of organ damage.

**Results:**

The survival of our patients at 1-, 3-, 5-, 10- and 15- years were 97.6%, 95.6%, 93.8%, 83% and 83% respectively. This survival rate is comparable with survival from developed countries for up to 5 years. At 10 years our survival is less than developed countries. The survival rate is better than previous data from India which was from one to two decades back.

Other than the number of criteria fulfilled for the diagnosis (The 1997 update of the 1982 revised ACR classification criteria for SLE), and use of Mycophenolate, Azathioprine or Cyclophosphamide none of the other parameters showed a significant correlation with survival in our study.

The mean survival time of the SLE patients with these different parameters are also calculated in this study.
The median duration of symptoms before a diagnosis was made for our cohort was 6 months, with 25 percentile having a diagnosis at 3 months and 75 percentile having a diagnosis at 18 months.

The common organ damages were cataract, seizures, end stage renal disease and diabetes mellitus.

**Conclusion:**

1. The five year survival of our south Asian cohort of SLE patients is 95.6% which is comparable with other published international cohorts. There is an improved survival of SLE patients in this south Asian cohort compared to previously published literature from the subcontinent.

2. The ten year survival of our cohort is 83% which is better than all previously published cohorts from south Asia, but is less than other cohorts from the developed world.

3. The commonest organ damage or its manifestations in our cohort of patients is seizures followed by diabetes mellitus, end stage renal disease and cataract in decreasing order of frequencies.

**Key words:** Survival in SLE, organ damage in SLE, Kaplan Meir survival curve in SLE
Aim

To find the survival rate and end organ damage of systemic lupus erythematosus patients of a South Asian population, in a developing country.

Objectives

• Find the survival pattern of a South Asian cohort of SLE patients in India.

• To identify factors that could influence the duration of survival

• Estimate the prevalence of permanent organ damage over different periods of time in this cohort of patients.
Introduction

Systemic Lupus Erythematosus (SLE) is one of the commonest disease entity with which patients come to any Rheumatology department. The other illnesses with which patients commonly reach the Rheumatologist are Seronegative spondyloarthropathy, Sjogren’s syndrome, other connective tissue diseases (viz. Rheumatoid arthritis, Scleroderma, Mixed Connective Tissue Disease, Inflammatory myositis), fibromyalgia, Crystal arthropathies, etc.

SLE is a disease predominantly of women, more so in the reproductive age group. In view of this nature of the time of life during which the disease starts and progresses, it has tremendous implications on the individual, the family and the society at large. The disease has been known for more than a century, and there are treatment modalities available for the disease for more than half a century. With major advances in the field of immunology, molecular biology and genetics, there has been a better understanding of the disease. Still there is a lot to be revealed on the etiopathogenesis of the disease and hence its management.

In the current scenario, the available treatment options have improved the quality of life and longevity of patients with the disease significantly. SLE being a multisystem disease, can have mucocutaneous, musculoskeletal,
neurological, psychiatric, cardiovascular, renal, hematopoietic, gastrointestinal, reproductive system, ophthalmic or pulmonary manifestations. This is compounded by the comorbidities due to the nature of the disease like infections and metabolic complications. Added to this are the effects of various treatment modalities on the different organ systems. In view of this the disease is very heterogeneous in its clinical presentation and profile. This would also mean the severity of the disease, the organ systems affected, the treatment required varies between individual patients.

In view of the multisystem nature of the disease, at the level of secondary or tertiary care patients with SLE could present to various specialties common ones being internal medicine, nephrology, dermatology, hematology or neurology in addition to Rheumatology. In a developing country like India where the health care is not generally well streamlined the approach to an individual patient may vary. Hence the outcome for the individual patient also depends on the expertise of the individual treating physician and health care team. This is compounded by the need for a multispecialty set up and more sophisticated investigations at least for some patients. As for any other illness, the mortality and morbidity of SLE is also influenced by the background morbidity and mortality in the community. This
in turn in a wider perspective is a reflection of the health care status of the community or country as the case may be.

Huge strides made in public health, availability of medical care and individual disease treatment has improved the outcome of many diseases including SLE. In spite of this there is long way to go before an optimum care of disease for all is achieved. As with many other diseases over the last three to four decades, for many patients, SLE has changed from an acute life threatening disease to a chronic illness requiring long term medical care including follow up, investigations and medications. This in turn has brought in issues of marriage, pregnancy, employment and employability. All these have social and financial implications on the individual, family and health care providers.

**The Indian Scenario**

Etiologically SLE has a strong genetic and environmental background. This in itself would mean that the behavior and outcome of the disease in India could be different from that of other ethnic, geographic and cultural groups. The rapid recent advances in medicine and great differences in availability and organization of health care between countries would mean that the inferences from one set of population need not necessarily be true for another population. This would mean
that to know about the behavior and outcome of Indian patients with SLE, we would need Indian data and inferences.

India being an ethnic mosaic would mean that there could be significant genetic differences within the population and hence the profile of diseases with a genetic basis. In addition to this are the economic differences within the population, which will affect the outcome of a disease particularly when the payment for medical treatment is at the point of care. Compounded to these factors is the wide divide in access to health care - urban vs rural or between the different states in India.

With regards to SLE there are few centers in India with specialized services catering to this group of patients.
Christian Medical College (CMC) Scenario

In CMC, SLE patients are predominantly managed by the Rheumatology department with inputs from Nephrologist, Radiologist, Intensivist, Infectious disease and other specialist as appropriate. Internal Medicine and Nephrology also manage SLE patients independently with input from Rheumatologist if required.

In terms of number of SLE patients we probably have one of the largest, anywhere in the world. Our patients are from a varied socioeconomic background. Geographically we have patients predominantly from South and Eastern India. We also get few patients from North and Western India, Bangladesh, Nepal, Bhutan and Maldives.
**Justification for the study**

There is very little data from India on the survival of SLE patients in India. Even the available data is reasonably old and hence may not reflect the current Indian situation on survival of SLE patients. There have been many changes in the health scenario in India which warrants evidence on the current scenario of SLE survival. India with its own unique ethnic, socio-economic and health care set up need to have information from our country to be meaningful to our patients. Mere extrapolation of data from other countries will have its own shortcomings.

Christian Medical College, Vellore being one of the major centers of Rheumatology in India and South Asia and has probably the largest cohort of patients with SLE, particularly so in the department of Clinical Immunology and Rheumatology in the institution. This information will be the closest available data on the survival of SLE patients in India. This could be used to prognosticate the SLE patients reaching a hospital in the country.
It would be useful, if possible to know the features at any given point which would help us to identify patients with a poor survival in terms of mortality and end organ damage.

For any disease, in addition to mortality one important aspect of interest to the patient and the health care team would be the morbidities due to the disease.

The morbidities have a major impact on the quality of life for the patient and their careers, their family, the need to accesses health care, the cost of health care.

Two major factors that determine morbidity in SLE are acute illnesses and permanent organ damage. The acute illnesses could be due to increased disease activity also called a disease flare, acute organ damage or associated complications like infections. Some possibilities of acute organ damage are pulmonary embolism, acute myocardial infarction, lupus celebrities, acute lupus nephritis etc. some of these being reversible.

The irreversible damages to the organ system – the permanent damages are major cause of morbidity and ads on to the mortality by themselves. These damages could be due to the disease itself or a complication of treatment for the disease. Cataract for example can be caused by steroid intake.
Seizures could be due to secondary antiphospholipid antibody syndrome in SLE, or cerebral involvement due to SLE. Persisting proteinuria more than 3.5 gm% or persistently raised creatinine are indicators of permanent renal damage.

Cardiac damage can manifest as angina pectoris or myocardial infarction. This can be due to the inflammatory nature of the disease per se or long term steroid use.

Osteoporosis and osteoporotic fracture can be due to steroid use. Avascular necrosis can be caused by secondary antiphospholipid antibody syndrome or long term steroid use. Another complication of long term use is steroid induced diabetes mellitus. It is known that there is an increased incidence of malignancy in SLE compared to age matched controls.
Review of literature

Diagnosis of SLE

SLE is a multisystem systemic autoimmune disease, with different systems affected to varying extent in each patient. One of the preliminary requirements for a study on SLE would be defining the patients. The diagnosis of SLE is based on classification criteria.

The classification criteria for a diagnosis of SLE have evolved from the early 1950’s to the second decade of the 21st century.

The American Rheumatism Association developed the first classification criteria in 1971\(^1\). This criteria was revised and published in 1982\(^2\). This criteria has 11 elements, a patient had to fulfill 4 out of the 11 in ordered to be labelled as SLE.

This criteria was revised in 1997, by the American college of Rheumatology (ACR) and is known as the “The 1997 update of the 1982 revised ACR classification criteria for SLE.”\(^3\)

In 2012, to include the new knowledge in the understanding of SLE, the Systemic Lupus International Collaborating Clinics (SLICC) group revised and
validated the ACR classification criteria called the “SLICC classification criteria for SLE”.

In the SLICC classification criteria for SLE, 17 criteria are identified. This criterion has a sensitivity of 94% and a specificity of 92%\(^4\). The patient must satisfy 4 criterion, including at least one clinical and one immunological criterion or the patient must have biopsy proven lupus nephritis with Antinuclear antibodies (ANA) or anti-double stranded DNA antibodies\(^4\) (Annexure II).

In our study cohort all the patients had a diagnosis of SLE made before 2012 and hence the 1997 update of the 1982 revised ACR classification criteria for SLE was used. This criterion has 86% sensitivity and 93 to 96% specificity\(^5\).

One of the limitations of the use of this criterion would be limited detection of mild cases of SLE, or new cases in the early stages of the disease\(^6\).
**Survival statistics**

In an ideal world, to determine the survival of patients with SLE, the general population should be surveyed for SLE and cases should be picked up right from the onset. The people affected and unaffected from SLE should be subsequently be followed up for health events and compared. This is a difficult and costly proportion.

Since this would not be a practical proposition, patients diagnosed with SLE can be subsequently followed up and their health events recorded up to death and this can be compared with a population matched for other variables which can influence health events. Even in this scenario, patients differ greatly in the length of time and severity of disease they have had before the diagnosis. There are multiple factors which could affect the outcome of the disease other than the biological factors connected to the disease. General quality of health in the background population, health seeking behavior in the population, quality and availability of health care, socioeconomic status, comorbid illnesses are some important ones among them. These limits the ability to generalize the observations derived from a given disease population. But the information derived from a specific clinic will be useful in evaluating its own outcome in
Managing patients. When a life table for survival analysis is made, two important issues to addressed are

(i) Definition of the starting point – in this study this is the point of diagnosis of SLE.

(ii) Length of follow up for those lost to observation, those still alive and under study, those who have died.

The commonly used methods for survival analysis are the life table, Kaplan-Meir, log rank and Cox model.

The analysis of the follow up of patients over long term is done in terms of a life table. From the life table, the proportion of patients surviving to various times since diagnosis is an important index of survival i.e. the survival rate at specific times. Other method is to make the survival curve which is based on the percentage of people existing at various time points. For duration of survival the median survival duration can be used for survival analysis. If less than 50 percent of the observations are uncensored and the largest observation is censored, the median survival time cannot be estimated, but the mean survival time is calculated.
The survival patterns help patients and treating physicians to ascertain what to expect in specific group of patients.

In survival analysis when the exact starting point of a disease is not known it is called left censoring. When the end time of the disease is not known it is called right censoring. In survival analysis one of the assumptions made is that survival pattern of those recruited at any time into the study are same. It is also assumed that different subgroups (eg. Socioeconomic status) have similar survival pattern. If the survival pattern is not similar they should be studied separately.

Kaplan-Meir\(^6\)

In this method of survival analysis is used when the patients are observed continuously and the exact duration of reaching the end-point or the time of dropout is known. The dropouts are considered in the analysis till the point of dropout and for the analysis after that they are not included. The proportion surviving at each unique time point is calculated from those patients available at that time point.

Ideally continuous observations of is to be used. In this way the exact time of survival or dropout is known for each patient. When the numbers of subjects are large periodic observations would be cost effective.
The plot of survival against time is called survival curve. The survival curve can be used to find the median survival time, quintiles and other measures of survival distribution.

**Causes of mortality in SLE**

SLE being a multisystem disease and predisposed for several comorbidities due to the disease itself and adverse events due to medications; finding out the exact cause of death in a given patient may be difficult. Before the middle of the twentieth century when there was no effective treatment for SLE, progressive disease activity and its complications was one the commonest cause of death in SLE\(^{10}\).

In the current scenario where the understanding and treatment of SLE has improved by leaps and bounds, severe lupus disease activity, infection, renal disease and cardiovascular disease are important causes of death in SLE. The survival rate of SLE has improved from less than 50% at 5 years to 92 – 98% in the first decade of this century as shown in the table from clinical and experimental rheumatology 2008;26(Suppl. 51) S 72 – 79.
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>No. of Patients</th>
<th>Location</th>
<th>Survival 5 Yrs</th>
<th>Survival 10 Yrs</th>
<th>Survival 15 Yrs</th>
<th>Survival 20 Yrs</th>
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<td>151</td>
<td>UAE</td>
<td>94</td>
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<td>NA</td>
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<td>Europe</td>
<td>95</td>
<td>92</td>
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<td>NA</td>
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<tr>
<td>Doria</td>
<td>2006</td>
<td>207</td>
<td>Italy</td>
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<td>93</td>
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<td>306</td>
<td>Japan</td>
<td>94</td>
<td>92</td>
<td>NA</td>
<td>77</td>
</tr>
<tr>
<td>Heller</td>
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<td>83</td>
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<td>276</td>
<td>South Africa</td>
<td>52-72</td>
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</tr>
</tbody>
</table>
Despite this SLE patients have a 2.4 to 3 fold increased risk of death compared with the general population\textsuperscript{9}. Lupus has a bimodal pattern of mortality\textsuperscript{9}.

Early mortality (< 1 Yr.) is due to severe disease activity and late mortality due to complications of long standing disease and treatment related complications.

\textbf{Reasons for improved survival}

Overall improvement in mortality in the general population has its impact on SLE as well. The table below shows the World Health Organization data on the survival of the general population in India in comparison to other developed countries.

In addition to the overall improvement in medical care, availability of antibiotics, antihypertensive, renal replacement therapy and the appropriate use of steroids, antimalarials and other immunosuppressive medications have improved survival of SLE patients.
Mortality studies – and survival data

International data

The five year survival of SLE was 50% in 1955\textsuperscript{7}. Currently the 5 year mortality is reported at 95\%\textsuperscript{11}. As discussed previously, part of this improvement is related to the improvement in health and survival of the population in general. Most of the data on the survival is from developed countries. Hence it is hard to judge the mortality in developing countries including India.

In addition to this is the fact that the average life expectancy in India is very different compared to North America or Europe.

According to the WHO data published in April 2011 life expectancy in India is: Male 63.8, female 67.3 and total life expectancy is 65.5 which gives India a World Life Expectancy ranking of 133\textsuperscript{12}.

In North America and Europe the average life expectancy is around 80 years. Even though there is contribution from high infant mortality in India, the life expectancy in India currently is less than what prevailed in the developed countries 20 years back\textsuperscript{12}. In addition to this fact is that non-Caucasians have a higher mortality in SLE compared to Caucasians.
<table>
<thead>
<tr>
<th>Country</th>
<th>Years</th>
<th>Male</th>
<th>Female</th>
<th>Both sexes</th>
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<tbody>
<tr>
<td></td>
<td>2011</td>
<td>64</td>
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<td>2000</td>
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<td>63</td>
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<td></td>
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<td>58</td>
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<td>1990</td>
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<td>79</td>
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<tr>
<td></td>
<td>2000</td>
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<td></td>
<td>1990</td>
<td>72</td>
<td>79</td>
<td>75</td>
</tr>
</tbody>
</table>
**Indian survival data**

There have been 3 published data on survival of SLE patients in India.

The first one was by Dr. Malaviya AN, Dr. Misra R et al from All India Institute of Medical Sciences, New Delhi in 1986 in Rheumatology International. This showed a five year survival of 68% and 10 year survival of 50% during the period 1981 to 1985\(^{13}\). The same centre with Dr Ashok Kumar, Dr. Malaviya AN et al Published survival data from 1986 to 1990 in Rheumatology International in 1992 which showed a similar outcome with no statistically significant improvement or any trend towards improvement compared to the previous 5 years\(^{14}\).

The third article was published from Christian Medical College, Vellore in the National Medical Journal of India in 1997 by Murali R, Jeyaseelan L, John L and Ganesh A. The cumulative percentage survival at 1,5 and 10 years was 89%, 77% and 60% respectively. The Markov chain predicted a life expectancy of 13.9 years\(^{15}\).
**SLE Survival in other Asian countries**

There have been studies which suggested that Asian patients have more organ involvement and mortality than Caucasians\textsuperscript{16}.

There have been other studies suggesting corrected for accesses to health care and socioeconomic status, the organ damage and mortality are comparable to Caucasians\textsuperscript{17}.

In a study published in Lupus 2011, among the Hong Kong Chinese, the 5 and 10 year cumulative survival of SLE patients was 92 and 83\% respectively. In this study renal damage was the most frequent disease related damage and musculoskeletal damage the commonest treatment related complication.

In this same paper an analysis of 514 SLE deaths showed that the most common cause of death was Infection (22\%) others being cancer 10\%, Cardiovascular (9\%), Cerebrovascular (5\%), complications and renal failure (7\%)\textsuperscript{18}.

In a previous study published in Rheumatology, in 2000, by the same group about mortality 186 patients were studied, diagnosed between 1992 and 1999. The 3-, 5-, and 7- year survival were 97, 93, and 93\% respectively\textsuperscript{19}. 
**SLE survival in other South Asian countries**

A retrospective review of the survival rate of 198 SLE patients was published in Lupus 2009 from the Aga Khan University Hospital, Karachi, Pakistan. The diagnosis of SLE was made between 1992 and 2005. This review showed survival rates of 3-, 5-, 10-, 15-, 20- year of 99, 80, 75, and 75% respectively. In this study, a multivariate analysis revealed renal disease was an independent risk factor for damage. By cox regression analysis it was seen that renal involvement and infection were independent risk factors for mortality.

In this analysis it was also shown that the mean duration of symptoms was 2.8 years before a diagnosis of SLE was made.

**Damage in SLE**

Death late in the course of SLE is due to accrued damage from the disease, its treatment and other co-morbidities.

The disease activity, particularly with respect to individual organs can result in specific organ damage and dysfunction. This results in increased morbidity. Thus the treatment of SLE focuses not only on preventing death but also reducing morbidity from the disease or its therapy.
Assessment of organ damage

In 1996 the SLICC group along with ACR, developed the SLICC/ACR Damage Index (SDI). The SDI assesses the damage in 12 body systems after onset of SLE. The SDI includes 41 items that could indicate organ failure, etc. The damage should be present for at least 6 months to be included in the SDI. The SDI is shown in annexure III. The damage is an independent outcome measure.

Indicators of Organ damage

The indicator of damage includes cataract, seizures, Proteinuria ≥ 3.5 g/day, renal failure, angina, myocardial infarction, osteoporosis with fracture or vertebral collapse, avascular necrosis, diabetes, malignancy.
Methodology

225 SLE patients who were admitted in the wards (Inpatients) of CMC, Vellore during the years 2007, 2008, 2009 and 2010 were recruited into the study. The clinical details and laboratory investigations of these patients at the time of admission were entered in the Excel sheet from their discharge summaries in the clinical work station.

The Clinical Work Station is a computer based application in which the patient data is entered and can be reviewed. In this patient data and patient’s reports like the discharge summary can be reviewed comprehensively.

These patients are being followed up in the department of Clinical immunology and Rheumatology, at varying intervals of time ranging from three monthly to two yearly. During the follow up visits these patients are assessed for disease activity and any organ damage. Clinical history, clinical physical examination and appropriate laboratory investigations are done towards this.

These patients are on different immunosuppressive medications which include steroids, hydroxychloroquine, cyclophosphamide, azathioprine or mycophenolate in different doses. The use of these medications could influence the survival and organ damage.
**Background of patients**

All these patients are from India, Bangladesh or Maldives visiting CMC Vellore for medical care.

The patients were recruited if they fulfill the 1997 update of the 1982 revised ACR classification criteria for SLE. They were recruited irrespective of the severity of the disease or specificity of indication for admission.

**Setting:**

These patients were followed up in the outpatient clinics of the Clinical Immunology and Rheumatology department or as inpatients, if they have been admitted at the time of review, based on the clinical condition. SLE patients on follow up, but not part of the cohort were not included in the study.

This was a cross sectional study followed up as a cohort

**Details of Research method:**

The participants of the study have a history, clinical examination and regular blood investigations done at the review visit. Each patient was assessed for organ damage. For patients who could not be seen on a specific follow up visit, the
outpatient scanned charts were screened for evidence of damage indices viz. cataract, seizure, proteinuria more than 3.5 gm/day, end stage renal disease, angina pectoris/angioplasty, myocardial infarction, osteoporotic fracture, avascular necrosis, diabetes mellitus or malignancy. These findings are recorded from the Clinical research form on to an excel sheet. These damages were recorded for 1-, 3-, 5-, 10-, and 15- years since diagnosis.

Each of these participants who have completed 1-, 3-, 5-, 10-, and 15- years are evaluated for a correlation between the survival and different parameters at admission including different forms of treatment.

For those patients for whom the last visit was more than 6 months before the time of analysis were contacted over the phone (mobile or land line) with regards to their survival status. The phone numbers were obtained from the hospital medical records of the patients.

With regards to damage indices the percentage of patients with permanent damage as indicate by the different parameters, at the end of 1-, 3-, 5-, 10- and 15-years are also calculated.
Details of data analysis

The data was initially entered into a Microsoft excel sheet. From this it was transferred to SPSS 16.0 and the analysis was done on SPSS 16.0.

The two, three, five, ten and fifteen year survival is calculated from a Kaplan-Meir survival curve created from this data. This curve can be used to calculate median survival rate at these number of years as well. Comparison of survival curves for different parameters were done using the log rank test.
Results

In our study 225 patients, who were admitted in Christian Medical College, Vellore between the years 2007 to 2010 were included. All of them fulfilled the 1997 update of the 1982 revised ACR classification criteria for SLE.

Gender distribution

Of these 208 (92.4%) were female and 17 (7.6%) were male.
**Median duration of symptoms before diagnosis**

Of the 225 patients, we had complete information on the exact time of onset of symptoms contributing to a diagnosis of SLE and the time of diagnosis of SLE for 165. In the remaining 60, the exact timing of onset of symptoms was not available.

The Median duration of symptoms before a diagnosis of SLE was made was 6 months with a range of 0 to 183 months.

The 25th percentile was 3 months and 75th percentile was 18 months.
**Deaths**

The total numbers of deaths recorded in the 225 patients were 17, during the follow up period.

**Survival analysis**

A Kaplan Meyer curve on survival analysis showed that the one year survival rate was 97.6%, the three year survival was 95.6%, five year survival rate was 93.8%, and the 10 and 15 year survival was 83%.
The mean survival period in SLE for our cohort of patients is 253.44 months with a standard error of 10.26 and 95% Confidence interval between 233.33-273.54.
Survival at 10 Years

In view of the very few patients at the 15th year follow up, the 15 year follow up may not be truly representative.

In view of increased censoring of values at 120 months (10 years), the survival curve for 10 years alone is taken and shown below
In view of the very few patient data available for survival beyond 10 years, the mean survival was calculated for 10 years. The mean survival period in SLE for our cohort of patients is 107.52 months with a standard error of 2.61 and 95% Confidence interval between 102.40-112.64.

We tried to look at the different factors which could predict difference in survival.
Gender and Survival

There were two deaths among the male patients and 15 deaths among the female patients.

The mean survival time for men was 151 months (SE 19.7, 95% Confidence Interval 112.45-189.83) while for women this was 258.04 months (SE 9.3, 95% Confidence Interval 240-276). This was not statistically significant. The p value was 0.734 [Log Rank (Mantel-Cox)].
ACR Criteria and Survival

By Log rank (Mantel-Cox), there was a significant correlation between the number of ACR criteria fulfilled at diagnosis with a p value of 0.008.
**S. creatinine at admission and survival**

The mean survival of the patients with a raised creatinine (>1.4 mg%) was 255.35 months (SE=11, 95% Confidence interval 233.8 – 276.9) while that for a creatinine < 1.4 was 121.15 months (SE=8.9, 95% Confidence interval 103.7 – 138.6). The p value was 0.209 [Log Rank (Mantel-Cox)], which is not significant.
Lupus Nephritis and survival

Of the 211 patients 132 had lupus nephritis while 79 did not have lupus nephritis. There were 9 deaths in those with lupus nephritis and 8 in those without lupus nephritis.

The mean survival of the patients with lupus nephritis was 258.18 months (Confidence interval 233.8 – 283.08) while for those without lupus nephritis was 196.39 months (Confidence interval 174.38 – 218.4). The p value was 0.43 [Log Rank (Mantel-Cox)], which is not significant.
Lupus Nephritis No. Total 132

- Not biopsied: 15
- Class 2: 2
- Class 3: 13
- Class 4: 28
- Class 5: 23
- Class 6: 51
The mean survival time for the class of Lupus nephritis is shown below

<table>
<thead>
<tr>
<th>Class</th>
<th>Mean Survival time (Months)</th>
<th>SE; 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class II (n=28)</td>
<td>79</td>
<td>9.9; 60-99</td>
</tr>
<tr>
<td>Class III &amp; IV (n=74)</td>
<td>63</td>
<td>5.3; 53-74</td>
</tr>
<tr>
<td>Class V (n=15)</td>
<td>90</td>
<td>21.6; 48-133</td>
</tr>
<tr>
<td>Class VI (n=2)</td>
<td>53</td>
<td>51.5; 0-153</td>
</tr>
</tbody>
</table>

These differences are not statistically significant
**Class II Lupus Nephritis**

There were 28 patients with Class II lupus Nephritis. 9 of them were treated with a second line agent while 19 were not treated with a second line agent. There were 2 deaths in the group without second line agent, none in the group with second line agent. The difference survival is shown in the graph below, but this is not statistically significant. [p 0.495 log rank (Cox-Mantel)]

![Survival Functions Graph](image)

1. Lupus nephritis with second line agent
2. Lupus nephritis without second line agent

42
Neuropsychiatric lupus and survival

21 patients had CNS lupus of which 2 died, while 189 did not have CNS lesions among them 15 died.

The mean survival time for patients with CNS lupus was 142 months (SE 23;95% Confidence Interval 97-187) while for those without CNS lupus is 258 months (SE 9;95% Confidence Interval 241-276). This was not statistically significant. The p value was 0.725 [Log Rank (Mantel-Cox)].
Secondary antiphospholipid antibody syndrome (APS) and survival

30 patients had antiphospholipid antibody syndrome while 178 did not have, 3 of the former died while 14 of the latter group.

The mean survival time for patients with APS is 119 months (SE 11; 95% Confidence Interval 231-275) while for those without APS is 253 months (SE 11; 95% Confidence Interval 231-275). This was not statistically significant.

The p value was 0.514 [Log Rank (Mantel-Cox)].
Survival with either cyclophosphamide or azathioprine or Mycophenolate

There were 83 patients who were on either cyclophosphamide or azathioprine or mycophenolate. There were 128 patients who were not on any of these at the time of admission. There were 3 deaths in the group on any of these second line agents, and 14 in the group not on second line agent.

Mean survival: Patients on a second line agent- 277 months (SE 6.6; 95% CI 264.4 to 290.3) Patients not on second line agent – 193 months (SE 11.2; 95% CI 170.8 to 214.8). This difference was statistically significant with a p value of 0.056 [Log Rank (Mantel-Cox)]

1.00  Survival in patients with cyclophosphamide or mycophenolate or azathioprine

0.00 Survival in patients without a second line agent.
## Organ damage at different time points

<table>
<thead>
<tr>
<th>SDI</th>
<th>1 Year</th>
<th>3 Year</th>
<th>5 Year</th>
<th>10 Year</th>
<th>15 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cataract</td>
<td>3/183(1.7)</td>
<td>4/144(2.8)</td>
<td>5/111(4.5)</td>
<td>1/26(3.8)</td>
<td>0(0.0)</td>
</tr>
<tr>
<td>Seizure</td>
<td>17/186(9.1)</td>
<td>14/150(9.3)</td>
<td>8/116(6.9)</td>
<td>4/27(14.8)</td>
<td>0(0.0)</td>
</tr>
<tr>
<td>Proteinuria (3.5gd)</td>
<td>1/182(0.5)</td>
<td>1/149(0.7)</td>
<td>0(0.0)</td>
<td>0(0.0)</td>
<td>0(0.0)</td>
</tr>
<tr>
<td>ESRD</td>
<td>6/185(3.2)</td>
<td>2/149(1.3)</td>
<td>6/116(5.2)</td>
<td>3/29(10.3)</td>
<td>0(0.0)</td>
</tr>
<tr>
<td>Angina/CABG/Plasty</td>
<td>1/183(0.5)</td>
<td>0(0.0)</td>
<td>0(0.0)</td>
<td>0(0.0)</td>
<td>0(0.0)</td>
</tr>
<tr>
<td>MI</td>
<td>0(0.0)</td>
<td>2/149(1.3)</td>
<td>1/114(0.9)</td>
<td>1/26(3.8)</td>
<td>0(0.0)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>0(0.0)</td>
<td>0(0.0)</td>
<td>0(0.0)</td>
<td>1/26(3.8)</td>
<td>0(0.0)</td>
</tr>
<tr>
<td>AVN</td>
<td>3/182(1.6)</td>
<td>6/148(4.1)</td>
<td>6/114(5.3)</td>
<td>0(0.0)</td>
<td>0(0.0)</td>
</tr>
<tr>
<td>DM</td>
<td>10/185(5.4)</td>
<td>9/150(6.0)</td>
<td>7/115(6.1)</td>
<td>4/26(15.4)</td>
<td>1/11(9.1)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>0(0.0)</td>
<td>0(0.0)</td>
<td>0(0.0)</td>
<td>1/26(3.8)</td>
<td>0(0.0)</td>
</tr>
</tbody>
</table>
Cumulative damage at various time points

<table>
<thead>
<tr>
<th>SDI</th>
<th>1 Year</th>
<th>3 Year</th>
<th>5 Year</th>
<th>10 Year</th>
<th>15 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cataract</td>
<td>3</td>
<td>6</td>
<td>9</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Seizure</td>
<td>17</td>
<td>24</td>
<td>24</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>Proteinuria (3.5gd)</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>ESRD</td>
<td>6</td>
<td>8</td>
<td>12</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Angina/CABG/Plasty</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>MI</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Osteoporotic fracture</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>AVN</td>
<td>3</td>
<td>6</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>DM</td>
<td>10</td>
<td>13</td>
<td>14</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>Malignancy</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

The commonest complication all thru the 10 years in our cohort of patients is Seizures. This is followed by diabetes mellitus, end stage renal disease and cataract.
**Discussion**

The following table shows a comparison of the survival data from our current study to the previous study from CMC, Vellore; All India Institute of Medical Sciences over two time periods; the Other South Asian study from Karachi, Pakistan and study from Hong Kong China.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>225</td>
<td>98</td>
<td>123</td>
<td>163</td>
<td>198</td>
<td>285</td>
</tr>
<tr>
<td>1 Year</td>
<td>97.6%</td>
<td>89%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>3 Year</td>
<td>95.6%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>99%</td>
<td>NA</td>
</tr>
<tr>
<td>5 Year</td>
<td>93.8%</td>
<td>77%</td>
<td>68%</td>
<td>68%</td>
<td>80%</td>
<td>92%</td>
</tr>
<tr>
<td>10 Year</td>
<td>83%</td>
<td>60%</td>
<td>50%</td>
<td>50%</td>
<td>75%</td>
<td>83%</td>
</tr>
<tr>
<td>15 Year</td>
<td>83%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>75%</td>
<td>80%</td>
</tr>
</tbody>
</table>
In our study the univariate analysis showed that the correlation was significant only between the number of ACR criteria fulfilling for the diagnosis of SLE and survival.

There was also a significant correlation between use of Mycophenolate or Cyclophosphamide or Azathioprine and survival compared to nonusers.

**Comparison with CMC Vellore study**

This study published in 1997, shows a survival less than our current study for all three years (1-,3-,and 5 Years).

*The possibilities for the improvement in the survival could be*

i. General improvement in the health indices in India as a whole.

ii. Improvement in care of patients with SLE in CMC itself

iii. During the previous study from CMC, SLE patients were managed in the General Medicine units, while in the current study all these patients were managed in the Clinical Immunology and Rheumatolgy unit.

iv. Availability of better amenities to treat complications

v. More widespread use of drugs like hydroxycholoroquine and more use of Mycophenolate for organ involvement.
Comparison with AllMS study\textsuperscript{13,14}

Both the studies from AllMS, are approximately 20 years back. There is major difference in the availability of health care in India during this period. There is considerable improvement in expertise and options of treatment for SLE available in India during this period. This could explain the significant improvement in survival in our study.

Comparison with Other South Asian Study\textsuperscript{20}

The study period of this study from Pakistan is closer to our study. The five and ten year survival is better in our cohort compared to the cohort from Karachi. The incidence of cataract and diabetes mellitus in our cohort of patients are more than the other cohort from Pakistan as well.

Comparison with study from Hong Kong China\textsuperscript{5}

The 5, 10 and 15 year survival in our cohort is comparable to this Chinese cohort. In comparison to the organ damage in the southern Chinese cohort of patients, diabetes mellitus and cataract are more common in our cohort than theirs. The CNS and renal damages were comparable.
Conclusion

1. The five year survival of our south Asian cohort of SLE patients in India at CMC, Vellore is 95.6% which is comparable with other published international cohorts.

   There is an improved survival of SLE patients in this south Asian cohort compared to previously published literature from the subcontinent.

2. The ten year survival of our cohort is 83% which is better than all previously published cohorts from south Asia, but is less than other cohorts from the developed world.

3. With improved survival of SLE patients the number of patients with SLE requiring medical care will be on the rise.

4. The commonest organ damage or its manifestations in our cohort of patients is seizures followed by diabetes mellitus, end stage renal disease and cataract in decreasing order of frequencies.
Bibliography


3. Dubois’ Lupus Erythematosus and Related Syndromes 8th edition Chapter 2 The Epidemiology of Lupus Pg 8).


[Pubmed:13233308]


10. Dubois' Lupus Erythematosus and Related Syndromes 8th edition. Chapter 57 Mortality in SLE Pg 668


12. WHO Global Health Observatory Repository accessed on 26th March 2013, 12.15pm


Annexure I

Clinical Research form- SLE Survival Analysis and Damage Indicators

Serial no.

**Demographics**

Name: Hospital number:
Age: Sex:

**Disease**

Date of first symptom:
Date of diagnosis of SLE:
Date of admission in CMC:
SLEDAI at admission:
SLEDAI at review:
Survival time in months:

<table>
<thead>
<tr>
<th>Treatment regime</th>
<th>Dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deflazacort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisolone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCQ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Mycophenolatemofetil
Mycophenolate sodium
  Azathioprine
  Cyclosporine
  Aspirin
  Warfarin
Acetrome

**SLICC/ACR**
  Cataract
  Seizures
  Proteinuria > 3.5 gm%
  Angina
  Myocardial Infarction
  Osteoporosis with fracture
  Avascular necrosis
  Diabetes Mellitus
  Malignancy
Annexure II
System Lupus International Collaborating Clinics/American College of Rheumatology
Damage Index for Systemic Lupus Erythematosus*

<table>
<thead>
<tr>
<th>Item</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ocular</strong> (either eye, by clinical assessment)</td>
<td></td>
</tr>
<tr>
<td>Any cataract ever</td>
<td>1</td>
</tr>
<tr>
<td>Retinal change or optic atrophy</td>
<td>1</td>
</tr>
<tr>
<td><strong>Neuropsychiatric</strong></td>
<td></td>
</tr>
<tr>
<td>Cognitive impairment (e.g. memory deficit, difficulty with calculation, poor concentration, difficulty in spoken or written language, impaired performance levels) or major psychosis</td>
<td>1</td>
</tr>
<tr>
<td>Seizures requiring therapy for 6 months</td>
<td>1</td>
</tr>
<tr>
<td>Cerebrovascular accident ever (score 2 &gt; 1)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Cranial or peripheral neuropathy (excluding optic)</td>
<td>1</td>
</tr>
<tr>
<td>Transverse myelitis</td>
<td>1</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td></td>
</tr>
<tr>
<td>Estimated or measured glomerular filtration rate&lt;50%</td>
<td>1</td>
</tr>
<tr>
<td>Proteinuria &gt;3.5 gm/24hours</td>
<td>1</td>
</tr>
<tr>
<td>Or</td>
<td></td>
</tr>
<tr>
<td>End-stage renal disease (regardless of dialysis or transplantation)</td>
<td>3</td>
</tr>
<tr>
<td><strong>Pulmonary</strong></td>
<td></td>
</tr>
<tr>
<td>Pulmonary hypertension (right ventricular prominence, or loud P2)</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary fibrosis (physical and radiograph)</td>
<td>1</td>
</tr>
<tr>
<td>Shrinking lung (radiograph)</td>
<td>1</td>
</tr>
<tr>
<td>Pleural fibrosis (radiograph)</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary infarction (radiograph)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
</tr>
<tr>
<td>Angina or coronary artery bypass</td>
<td>1</td>
</tr>
<tr>
<td>Myocardial infarction ever (score 2 if &gt; 1)</td>
<td>1(2)</td>
</tr>
<tr>
<td>Cardiomyopathy (ventricular dysfunction)</td>
<td>1</td>
</tr>
<tr>
<td>Valvular disease (diastolic murmur, or systolic murmur &gt;3/6)</td>
<td>1</td>
</tr>
<tr>
<td>Pericarditis for 6 months, or pericardectomy</td>
<td>1</td>
</tr>
</tbody>
</table>
**Peripheral vascular**
- Claudication for 6 months 1
- Minor tissue loss (pulp space) 1
- Significant tissue loss ever (e.g. loss of digit or limb)(score 2 if > 1 site) 1(2)
- Venous thrombosis with swelling, ulceration, or venous stasis 1

**Gastrointestinal**
- Infarction or resection of bowel below duodenum spleen, liver, or gall bladder ever, for cause any (score 2 if > 1 site) 1(2)
- Mesenteric insufficiency 1
- Chronic peritonitis 1
- Stricture or upper gastrointestinal tract surgery ever 1

**Musculoskeletal**
- Muscle atrophy or weakness 1
- Deforming or erosive arthritis (including reducible deformities, excluding avascular necrosis) 1
- Osteoporosis with fracture or vertebral collapse (excluding avascular necrosis) 1
- Avascular necrosis (score 2 if > 1) 1(2)
- Osteomyelitis 1

**Skin**
- Scarring chronic alopecia 1
- Extensive scarring or panniculum other than scalp and pulp space 1
- Skin ulceration (excluding thrombosis) for > 6 months 1
- Premature gonadal failure 1
- Diabetes (regardless of treatment) 1
- Malignancy (exclude dysplasia) (score 2 if > 1 site) 1(2)

*Damage (nonreversible change, not related to active inflammation) occurring since onset of lupus, ascertained by clinical assessment and present for at least 6 months unless otherwise stated. Repeat episodes must occur 6 months apart to score 2. The same lesion cannot be scored twice.*