Trends and predictors of mortality in childhood onset lupus in a single North-Indian centre over 23 years: a retrospective study

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Abstract

Objective

Systemic lupus erythematosus has been shown to be associated with worse survival in developing countries in adults and children. However, there are limited data on causes of death and time-trends of mortality in childhood lupus from developing countries. The aim of this study was to determine any changes in occurrence (time-trends) and aetiology of mortality over 23 years at our centre and to determine the risk factors associated with mortality.

Methods

This retrospective study included patients with childhood onset lupus (fulfilling ACR 1997) who were diagnosed at the Paediatric centre of a North-Indian federally funded university hospital from 1991 to 2013 and were below 14 years of age at presentation (age cut-off used to register patients in the Paediatric centre). Patients were divided into three cohorts based on their year of presentation, i.e. 1991-1998, 1999-2006 and 2007-2013 to evaluate differences in survival over time at our centre. Survival was estimated by Kaplan-Meier analysis and predictors of mortality were analysed by Cox-regression. A worst-case-scenario was also calculated by assuming patients lost to follow-up as not survived.

Results

This study included 122 children (F:M=3:1) with childhood onset SLE having a mean age of onset of lupus and presentation to our centre being 9.2±2.7 years and 10.5±2.7 years. During a mean follow-up of 4.8±4.5 (range 0–20) years, 24 children (20%) died. Survival rates at 1, 5 and 10 years was 88.3, 77.5 and 70.9%. In the worst case scenario, the survival was 78.3, 59.5 and 38.8% respectively. Only serum creatinine was significantly associated with time-to-event (death) (Hazard ratio 2.9; 95% CI: 1.3–6.8; p=0.008). There was a significant improvement in survival in patients that presented between 1999-2006 compared to patients who presented in 1992-1998 (p=0.03). Among the patients who died, 11 died at the time of first admission, whereas 13 died later. Major cause of mortality in former was infection and active disease, and in the latter was end-stage renal disease.

Conclusion

In this single-centre study, childhood onset lupus was associated with a mortality of 20%, with the major predictor of mortality being serum creatinine at presentation. A comparison of different cohorts of patients found an improvement in survival over time at our centre.

Key words

childhood sytemic lupus erythematosus, mortality, infection, disease activity

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Introduction

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disorder with childhood onset accounting for15–20 percent (1). Previous studies in adults have shown a bimodal pattern of mortality in patients with SLE, with early deaths (<2 years) often due to active SLE or infection while late deaths (>2 years) due to atherosclerotic vascular disease, reactivation of SLE or infections (2). Recent studies have reported a considerably improved 5 and 10 year survival rates of 94% and 90% in children with lupus, mainly from developed nations and some even from developing South East Asian countries (3, 10). However, there is paucity of data on the survival pattern and causes of mortality in Indian children with lupus. We had published a study on the mortality pattern on Indian lupus children from our centre twelve years back (4). The aim of this study was to determine any changes in occurrence (time-trends) and aetiology of mortality over 23 years at our centre and to determine the risk factors associated with mortality.

Methods

This study included patients with childhood onset lupus who presented between 1991 to 2013 to our Paediatric centre, which is a part of a North-Indian federally funded university hospital. Patients were included in this study if they fulfilled the ACR 1997 revised criteria for systemic lupus erythematosus and were below the age of 14 years on presentation (this is the age cut-off used in our hospital to register patients at the paediatric centre) (5). Clinical data was extracted from the medical records. This included demographic and disease data, including age at presentation, gender, age of onset, duration of disease (from onset of first symptoms attributable to lupus to time of presentation at our centre), serum creatinine at presentation, duration of follow-up (time between presentation at our centre to last follow-up) and cause of death. The cause of death was categorised into infection, activity, both or complications related to end-organ damage (end stage renal disease). In addition, we categorised patients who died into two categories - died at first presentation to our centre or those who died later to look at differences between these two patient groups in terms of cause of death. We also looked at change in mortality over time at our centre. For this purpose, we divided the entire group into three cohorts based on the year they presented to our centre: 1991–1998, 1999–2006 and 2007–2013 and calculated survival rates for different time periods.

Comparison of groups was done using the independent *t*-test and chi-square test for continuous and categorical variables respectively. Survival was analysed using Kaplan-meier analysis and predictors of time-to-event (death) were determined among baseline characteristics using cox-regression analysis. For this purpose, we first looked at univariate predictors and then looked at predictors that remained significant on multivariate analysis (6). Comparison between different cohorts (as per year of presentation) was done by log-rank test. Statistical analysis was done using SPSS (Released 2007. SPSS for Windows, v. 16.0. Chicago, SPSS Inc).

Results

This study included 122 patients after excluding 3 children who did not fulfil the ACR 1997 criteria for systemic lupus erythematosus. The female: male ratio was 3:1 with mean age of onset of lupus and presentation to our centre being 9.2±2.7 and 10.5±2.7 years respectively. Anti-nuclear antibody was positive in most (120/122, 99%) and anti-dsDNA was positive in 71/93 (76%). Common clinical features at presentation and cumulatively was fever and rash. During a mean follow-up of 4.8±4.5 years (range 3 months to 20 years), twenty-four children (20%) died. There was no difference in the age of onset, duration of illness, duration of onset to diagnosis and treatment received between those who died compared to those who survived. However, renal involvement at initial diagnosis (as well as cumulatively), specifically, presence of azotemia, hypertension, haematuria and proteinuria was significantly higher in the children who died compared to those who survived (Table I).

Table I. Clinical features and treatment in children at initial presentation to our centre and cumulative in course of their illness comparing differences between survivors and those who died (Significant differences are marked).

	Total (n=122)		Survivors (n=98)		Deaths (n=24)	
	Initial	Cumulative	Initial	Cumulative	Initial	Cumulative
Gender (F:M)	91:31	-	73:25	-	18:6	-
Age at onset (Mean ±SD)	9.2 ± 2.7	-	9.3 ± 2.8	-	8.7 ± 2.2	-
Fever, n (%)	106 (87)	109 (89)	84 (85.7)	87 (88.8)	22 (91.7)	22 (91.7)
Arthritis, n (%)	46 (38)	64 (53)	34 (34.7)	50 (51.0)	12 (50)	14 (58.3)
Malar rash, n (%)	67 (55)	84 (69)	53 (54)	67 (58.2)	13 (54.2)	17 (70.8)
Oral ulcers, n (%)	53 (43)	77 (63)	42 (42.9)	62 (53.1)	11 (45.8)	15 (62.5)
Photosensitivity, n (%)	39 (32)	61 (50)	28 (28.6)	47 (47.9)	11 (45.8)	14 (58.33)
Alopecia, n (%)	20 (16)	24 (20)	19 (19.4)	22 (22.4)	1 (4.1)	2 (8.3)
Serositis, n (%)	12 (10)	28 (23)	8 (8.1)	18 (18.4)	4 (16.7)	10 (41.7)
Haematological, n (%)	46 (38)	73 (60)	36 (36.7)	56 (57.1)	10 (41.6)	17 (70.8)
CNS, n (%)	21 (17)	35 (29)	17 (17.3)	28 (28.6)	4 (16.6)	8 (33.3)
Renal, n (%)	55 (47.5)	74 (61)	38 (38.8)	52 (53.1)	17 (70.8)*	22 (91.7)*
Azotemia, n (%)	15 (12.3)	-	5 (5.1)	-	10 (41.7)*	-
Hypertension, n (%)	27 (22.1)	-	17 (17.3)	-	10 (41.7)*	-
Haematuria, n (%)	53 (43.4)	-	39 (39.8)	-	14 (58.3)*	-
Proteinuria, n (%)	55 (47.5)	-	26 (26.5)	-	17 (70.8)*	-
Steroids, n (%)	122 (100)	--	98 (100)	--	24 (100)	--
Cyclophophamide, n (%)	39 (31.9)	--	29 (29.6)	--	10 (41.7)	--
Azathioprine, n (%)	30 (24.6)	--	25 (25.5)	--	5 (20.8)	--
Mycophenolate, n (%)	7 (5.7)	--	6 (6.1)	--	1 (4.1)	--

*p<0.05.

Survival rates in our cohort was 88.3, 77.5 and 70.9% at 1, 5 and 10 years respectively (Fig. 1a). On univariate analysis (by Cox proportional hazard analysis), among variables at presentation whose data was available (including age at onset, gender, disease duration, CNS involvement, haemoglobin, hypertension and serum creatinine), only serum creatinine was significantly associated with time-to-event (death) (Hazard ratio 2.9; 95% CI: 1.3–6.8; p=0.008). Similarly on multivariate analysis of variables also, only serum creatinine at baseline was associated with time to event (death). On worst-case analysis, survival rates were 79.3, 59.5 and 38.8% at 1, 5 and 10 years, respectively.

Among the children who died, 11 died at the initial admission to the hospital whereas 13 died at later follow-up. There were significant differences between these groups. The major cause of mortality in the former was presence of both infection and active disease, whereas in the latter, it was end-stage renal disease and its complications.

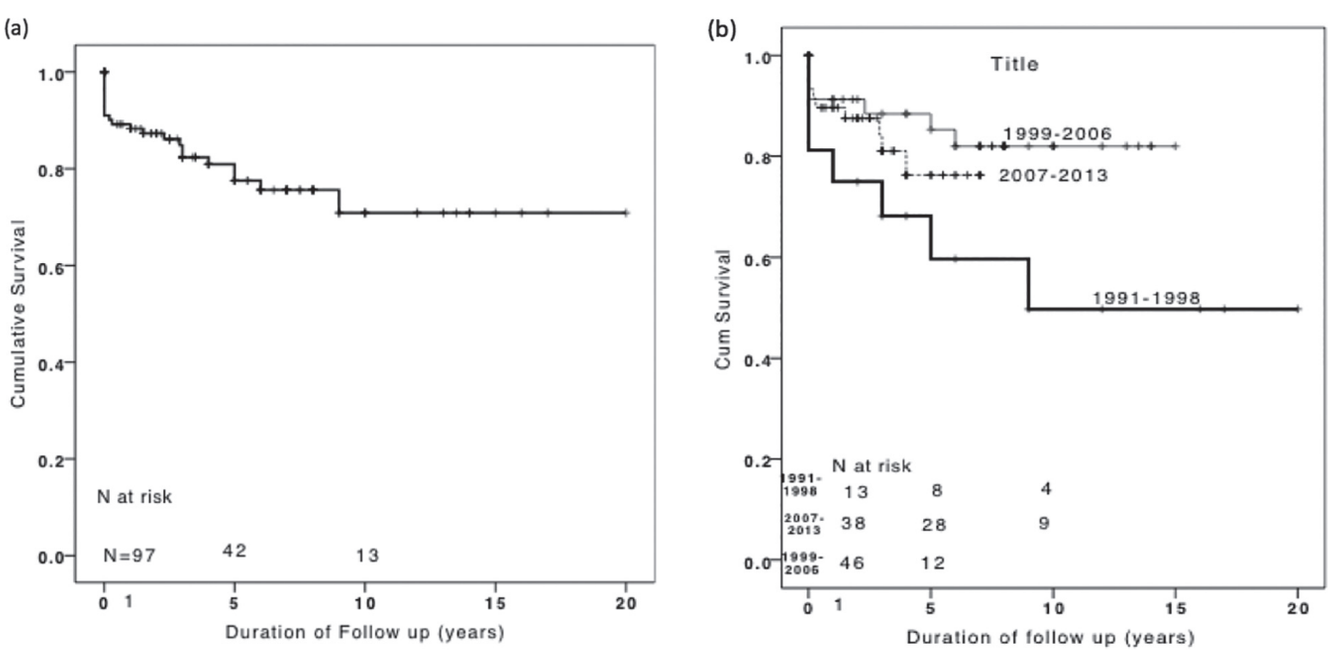

Fig. 1. **a**: Overall patient survival of 122 patients. **b**: Survival trends according to the three time periods (1991-1998, 1999-2006, 2007-2013).

Table II. Broad categories in causes of death in the cohort of children with SLE (*p<0.05).

Cause of death	Died at initial visit (%)	Died on later follow-up (%)	Overall (%)
Infection + Active disease	7 (63.6)*	2 (15)	9 (37.5)
Active disease only	3 (27.3)	2 (15)	5 (25)
Infection only	0	3 (23)	2 (8)
End-stage renal disease	0	4 (31)	4 (17)
Others	1 (9)	2 (15)	3 (13)
Total	11 (100)	13 (100)	24 (100)

Table III. Types of infections that contributed to death in this cohort of childhood lupus patients.

Infection contributing to death	n. of patients
Tuberculosis*	3
Disseminated fungal infection (Aspergillosis1; Zygomycosis* (with disseminated CMV) 1)	2
Septicaemia	
Gram negative (E.coli=2)	2
Polymicrobial (Staphylococcal+ Acinetobacter + Klebsiella + Enterococcus=1; Klebsiella+ Pseudomonas=1; Salmonella + Enterobacter=1)	3
Gram positive (Staphylococcus=1)	1
Infective Endocarditis (Acinetobacter)	1
Total	12

*concomitant gram negative septicaemia.

(Table II) Among 12 patients with infection contributing to death, sepsis was the major cause and it was commonly polymicrobial or gram negative. (Table III) All of these children had hypergammaglobulinaemia, and 5 had lymphopenia. Among the 14 cases with disease activity contributing to death, organs involved included lupus nephritis in 12, neuropsychiatric lupus in 7, myocarditis in 2 and diffuse alveolar haemorrhage and macrophage activation in 1 each. Seizure was the commonest presentation of neuropsychiatric lupus. CSF examination in all the seven children were normal. Neuroimaging showed cerebral atrophy with ventricular dilatation in 2 children and extensive white matter demyelination in another, in the rest imaging was normal. Imaging in the three children with tuberculosis showed multiple tuberculomas in 1 child, chronic infarct with dilated ventricles in one and basilar exudates in the third. CSF was positive for acid fast bacilli in two and ADA was highly elevated in third child whose neuroimaging showed basilar exudates. Immunisation status in all patients had included BCG vaccination, however, none had received pneumococcal vaccine. Cotrimoxazole prophylaxis was not routinely given to immunosuppressed patients at our centre. All children were routinely screened for tuberculosis by a chest radiograph and Mantoux test, and one patient was detected to have pulmonary tuberculosis at presentation to our centre, and one child had history of previous proven treated tuberculosis. On dividing the patients by the year in which they presented, 16 children presented between 1991–1998, 46 children in the 1999-2006 period and 60 children in the 2007–2013 period. The mean follow-up period was 7.2±7.2 years (2840 patient years), 6.7±4.5 years (12,374 patient years) and 2.8±2.2 years (9480 patient years) respectively. Comparison of treatment given to these children according to their year of presentation did not show any statistical significance. On a comparison of the different cohorts by time of presentation, there was a significant improvement in survival in the patients that presented later (1999–2006) compared to the patients who presented in the earlier time period (1992-1998) (p=0.03) (Fig. 1b). This was mainly contributed by the major decline in the proportion of patients who died at initial presentation from 25% to 8% in 1992-1998 and 1999–2006 respectively.

Discussion

This retrospective study from a federally funded university hospital in a resource poor country found mortality occurred in one-fifth of all children with SLE (below 14 years at presentation), with almost half occurring in the initial visit. A decade back, we had reported mortality at our centre in these group of patients to be 30% (4). Overall, our results show a lower survival compared to some North American or European studies (3, 6). The mortality rate of 20% is higher than that reported from some recent series from America, Europe, Asian Chinese (Taiwanese) and Middle Eastern studies (7-11). However mortality similar to ours has also been reported in Thai children (12). A summary of some recent and older studies on survival and mortality in childhood lupus reveals this difference in mortality across centres (Table IV). Some of the reasons speculated to contribute to poorer outcome in developing country centres like ours include general issues like lack of access to tertiary medical care with consequent delays in diagnosis and treatment as well as some centre specific issues. Indeed, it has been shown earlier that the time to diagnosis is inversely associated with disease activity in lupus (13). Our centre is a federally funded tertiary care hospital, with an institutional policy of not denying admission to any patient. Many of our patients do not have financial resources or insurance coverage and are often admitted through the emergency services when suffering from a life threatening advanced stage of illness.

In a study that was reported from our centre in childhood lupus a decade back, uncontrollable disease activity was found to be responsible for 60% of the deaths, with 40% of the children having concomitant hospital acquired infection (4). In the current study, severe active lupus with co-existing infection, either community acquired or hospital acquired were still responsible for almost all the deaths. The most common

Table IV. Summary of recent major studies on survival and mortality in children with lupus.

Author, year (reference)	Country / Ethnicity	n. (M:F)	Follow- up	Patient Survival			Died (%)
				1/2 yrs	5 yrs	10 yrs	
Present study, 2015	Chandigarh, India	122 (1:3)	4.75 ± 4.5	88	77	70	24 (20)
Son *et al*.*, 2014 (7)	Massachusetts, USA*	2775 (1:4.5)	-	-	-	-	41 (1.5)
Hamzi *et al*., 2014 (24)	Saudi Arabia	48 (1:15)	15 ± 4	-	-	-	3 (6.3)
Lee *et al*., 2013 (10) (11)	Taiwan	164 (1:5.5)	7.2 ± 3.8	-	95.4	94	15 (9.1)
Vachvanichsanong *et al*., 2010 (11, 12)	Thailand	213 (1:4)	3.6	88	76	64	51 (23.9)
Hari *et al*.¶, 2009 (21, 25)	Delhi, India	54 (1:2.8)	3.1	88	-	-	9 (16.7)
Gomez *et al*., 2008 (22, 26)	Latin America	238 (1:9)	1.7 -		-	-	9 (3.8)
Wong *et al*.¶, 2006 (23, 27)	Hong Kong, China	128 (1:15)	5.7 ± 3.6	-	94	91.8	5 (3.9)
Bogdanovic *et al*.¶, 2004 (8)	Serbia	53 (1:7.8)	4.8 ± 3.4	-	88.6	-	4 (6)
Singh *et al*., 2002 (4)	Chandigarh, India	31	3.2				10 (32)
Hagelberg *et al*., 2002¶ (9)	Toronto, Canada**	67 (1:3.8)	11	-	97	-	4 (5.9)
Baqi *et al*.¶, 1996 (24, 28)	New York, USA***	56 (1:5.2)			44	29	9 (16)

*White (39.6%); African American (35.4%); Asian (5.3%). Data only on number of hospital admissions for patients aged 3 to 18 years with diagnosis of SLE. **Caucasians 53.7%; non Caucasians (46.3%). ***African American (64.3%), Hispanic (21.4%), White (8.9), Others (5.4%).
¶Children with lupus nephritis age up to 18 years.

infection contributing to mortality in the initial period was sepsis, commonly polymicrobial. This susceptibility to infection may be caused by lupus activity *per se*, use of corticosteroids and other immunosuppressives and renal failure (14). Also studies have shown that secondary bacterial infection gives rise to greater mortality as compared to other infections (15). In our cohort also, gram negative septicaemia (alone or polymicrobial) was common, similar to other studies in Asian patients with Lupus (16). A study on a large cohort of Chinese lupus patients have demonstrated lowest survival rates for infection with Pseudomonas, Klebsiella And Acinetobacter with polymicrobial infection being more frequent as compared to single pathogen (17). Fungal infections and tuberculosis were other infections found in our cohort. Invasive fungal disease is a life-threatening opportunistic infection, usually observed in the immunocompromised host (18, 19).Aspergillus infection has been found to be the most frequently identified opportunistic invasive fungal infection in SLE patients, followed by Cryptococcus and Candida in a previous study (20). Among patients who died in our study, manifestations of lupus activity were seen in the form of lupus nephritis, neuropsychiatric SLE and myocarditis. Some of these have been autopsied and reported earlier as clinico-pathologic conferences (21).

This study found that survival of children with SLE at our centre has signficantly improved on comparing periods between 1991–1998 and 1999–2006. However, there was no difference with the most recent cohort, probably due to limited follow-up. This fall in mortality could be due to variety of reasons. First, it parallels a rise in the number of cases of lupus seen at our centre. As compared to the period between 1991–1998, when 16 children were seen, in the period between 1999 to 2006, 46 children were seen. This may suggest an increase in milder cases due to earlier referral from local physicians (due to improved recognition and knowledge) or an improvement based on experience of our centre in dealing with these children. The fact that less number of children die in the initial visits in more recent times supports the former contention. With the improvement in patient survival, studies from developed nations in the West and even some from South East Asia have reported cardiovascular illnesses and its complication to be a major determinant of mortality in the long term outcome (22-23). However in our study, we did not observe a single patient dying of cardiovascular complication. The reason could be because of the extremely young age group of our cohort and limited follow-up. This being a retrospective study had certain limitations like absence of disease activity scores or complement levels uniformly in all patients. A significant proportion of patients were lost to follow-up and might overestimate survival. To overcome this, we have also calculated a worst case scenario for this reason. Also, we have tried to include common factors influencing mortality as reported in other studies, but some factors were excluded due to incomplete data like complement levels, socioeconomic data, antiphospholipid antibodies and disease activity scores. Finally, it may be argued that infections being a common cause of mortality, vaccinations or cotrimoxazole prophylaxis would be beneficial in our immunosuppressed patients and have a favourable cost-benefit ratio, and this policy may be implemented in the future.

To conclude, this study from a tertiary care hospital suggests that mortality in children with lupus in some centres in developing countries still remains high at 20% with the existing care. Major causes of death are active SLE with superadded infection at initial presentation. The major determinant of mortality in the long term is the occurrence of end stage renal disease. However despite all the constraints of a resource poor setting, there seems to be a reduction in mortality over time. Lastly, to reduce patient mortality, an overall improvement in the standard of care including early diagnosis and referral along with early detection of infection are required.

Key messages

- Childhood-onset lupus from this federally funded referral centre in North India is associated with a higher mortality as compared to those from developed countries. Delays in diagnosis and referral at the periphery, difficulty in accessing healthcare because of poverty and geographic isolation are some of the factors that contribute to this increased mortality in these children.
- Infection and active disease still remain the most common causes of death.
- However, there has been a significant improvement in survival in the more recent patients enrolled.

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