Lupus nephritis in Chinese children – a territory-wide cohort study in Hong Kong

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Abstract

We reported a multicentre study of Chinese children with SLE nephritis in Hong Kong. Cases were included if they fulfilled the ACR criteria, had significant proteinuria or casturia, were Chinese before 19th birthday, and diagnosed between January 1990 to December 2003. Investigators in each centre retrieved data on clinical features, biopsy reports, treatment and outcome of these patients. There were 128 patients (8 boys, 120 girls; aged 11.9±2.8 years). About 50% presented with multisystem illness and 40% with nephritic/nephrotic symptoms. Six percent had negative anti-dsDNA antibodies. Renal biopsy revealed WHO Class II, III, IV and V nephritis in 13 (10%), 22 (17%), 69 (54%), and 13 (10%) patients respectively. The clinical severity of nephritis cannot accurately predict renal biopsy findings. Follow up ranged from 1 to 16.5 years (mean±SD = 5.76±3.61 yrs). Overall five patients died (due to lupus flare in two, cardiomyopathy in one, infections in two). Four patients had endstage renal failure (one died during a lupus flare). All deaths and ESRF occurred in Class IV nephritis group. Chronic organ damages were infrequent in survivors. The actuarial patient survival rates at 5-, 10- and 15-years were 95.3%, 91.8%, and 91.8% respectively. For Class IV nephritis patients, the survival without ESRF at 5-, 10-, and 15-years were 91.5%, 82.3%, and 76% respectively. The survival and chronic morbidity of Chinese SLE children were comparable to previous published reports.

Key-words:

Systemic lupus erythematosus; nephritis; Chinese; children; prognosis; mortality; morbidity; damage index

Introduction

Systemic lupus erythematosus (SLE) is the commonest autoimmune disorder with renal involvement that leads to chronic kidney disease. About 10-15% of SLE patients had their diagnosis made in childhood.[1] It was reported that childhood-onset SLE patients were different from adult patients, in that they have more nephritis, more central nervous system involvements,[2] and more thrombotic thrombocytopenic purpura (TTP).[3] Moreover, some authors reported a poorer outcome in paediatric SLE patients[4] while others did not observe such a difference.[5;6] There were also reported ethnic differences in the incidence and severity of SLE patients such that African Americans and Hispanic patients were worse than the White patients.[7-9] Most of these reports were small case-series and limited by referral bias as they came from tertiary paediatric centres. There were only scanty data on SLE nephritis in the Chinese population. Most publications were on adult Chinese patients[10-12] and the only report on Chinese children was made a decade ago from a referral centre.[13] This study aimed at providing updated data on SLE nephritis in Chinese children, by descirbing a territory-wide cohort of unselected paediatric patients in Hong Kong. In addition to the clinical features and treatment, the mortality and long term morbidity of these children were also reported.

Patients and Methods

Hong Kong has a total population of 6.7 million, of which 95% were Chinese, and 21.7% were aged 18 years or below. Since 1990, the Hospital Authority of Hong Kong operated all the public hospitals in Hong Kong and covered 90-94% of patient services in

the territory. All eleven paediatric units in the Hospital Authority hospitals participated in this retrospective study. Patients diagnosed to have SLE nephritis between 1st January 1990 to 31st December 2003 were retrieved from hospital/departmental databases and crosschecked with renal pathology databases. Patients were included if 1) they were Chinese with SLE diagnosed before their 19th birthday; 2) they fulfilled the American College of Rheumatology criteria for diagnosis of SLE; 3) they had persistent significant proteinuria (urine protein/creatinine ratio of 0.5 mg/mg or more) or had active urine sediments with erythrocytes and casts; and 4) they had at least one year of follow up data. For the purpose of reviewing a homogeneous Chinese cohort, patients of other ethnicity were excluded.

The record of each patient was reviewed and data were extracted into a standard questionnaire. Data collected included age at first presentation, at diagnosis, and onset of nephritis; the clinical features and worst laboratory results within 3 months of diagnosis; the renal biopsy reports; induction and maintenance treatment and their response; the clinical and renal status at one year after nephritis, their complications, and outcome at last follow up.

Haematuria was defined as positive haemastix or 10 erythrocytes per high power field on urine microscopy on 3 occasions. Proteinuria was defined as urine protein to creatinine ratio in mg/mg (Up/c) of 0.2 or more on 3 occasions. Glomerular filtration rate (eGFR) was estimated by Schwartz formula from body height and serum creatinine. Nephrotic syndrome was defined as the presence of oedema, massive proteinuria (Up/c > 2) and hypoalbuminaemia (serum albumin < 25 g/L). Nephritic syndrome was defined by haematuria, hypertension and renal impairment with eGFR <90 ml/min/1.73m^2.

Hypertension was defined as persistent elevation of blood pressure above 95th percentile for age and gender, and those requiring anti-hypertensive treatment. Antinuclear antibody (ANA) was measured by indirect immunofluorescence and a titre of 1/80 or higher was reported as positive. Anti-double strand DNA antibodies (anti-dsDNA) was measured by enzyme-linked immunosorbent assay (ELISA) using commercial kits and reported positive when it was above the quoted reference ranges. All samples for anti-Ro, La, and Sm antibodies were measured by counter-current immunoelectrophoresis in a single university laboratory with in-house reference sera characterised by comparison with CDC reference sera for the respective antibody. Anti-cardiolipin IgG and IgM were studied by ELISA with upper limits of normal as 15 GPL/ml for IgG and 13 MPL/ml for IgM.

All renal biopsy specimens were examined by light microscopy with standard staining, immunofluorescence, and electron microscopy. They were interpreted by renal pathologists in individual hospitals and were classified according to the World Health Organization (WHO)[14]: Class II being mesangial glomerulonephritis; Class III being focal proliferative glomerulonephritis; Class IV being diffuse proliferative glomerulonephritis; Class V being membranous nephropathy. For the purpose of analysis of presenting features and outcome, mixed Class III+V and Class IV+V nephritis were grouped as Class III and Class IV respectively, while Class II+V nephritis was grouped with pure Class V nephritis.

Patients were categorized according to the induction therapy they had received for their nephritis: In Group 1, high-dose prednisolone at 2 mg/kg/day was given till remission. In Group 2, patients received high-dose prednisolone plus azathioprine (AZA) at 1-3 mg/kg/day as tolerated. Group 3 patient were treated with high-dose prednisolone

plus oral cyclophosphamide (POCYC) at 2 mg/kg/day for 3-6 months. Group 4 patients received high-dose prednisolone plus monthly intravenous cyclophosphamide (IVCYC) pulses at 500-1000 mg/m^2 for 6 months. In Group 5, high-dose prednisolone plus mycophenolate mofetil (MMF) at 750-1200 mg/m^2/day were given. Group 6 patients received high-dose prednisolone plus cyclosporine A (CSA) at 3-5 mg/kg/day. In all groups, oral prednisolone doses were tailed down gradually as maintenance therapy. Group 3 patients were switched to azathioprine, while Group 4 patients received either quarterly IVCYC for 2 years or MMF or AZA as maintenance. Patients in other groups also received the same induction cytotoxic agent for maintenance.

The renal status at one year after onset of nephritis was described as: complete remission CR (having no clinical symptoms of activity, Up/c <0.2, normal serum albumin and eGFR); partial remission PR (remission of clinical symptoms, >50% improvement in Up/c or eGFR); and non-response NR (no change in clinical status and <50% improvement in Up/c or eGFR). Relapses were defined as recurrences of clinical disease and worsening of C3/C4 and serology and requiring clinicians to increase therapy to high dose prednisolone (1mg/kg/day) or adding another immunosuppressive drugs for control. Additional drugs used for relapsers were recorded.

The clinical activity at diagnosis and one year after nephritis were assessed by Systemic Lupus Erythematosus Disease Activity Index (SLEDAI).[15] The SLEDAI is a weighted, cumulative index and has 24 attributes grouped into 9 organ systems. Each attribute when present within 10 days before the assessment time was given a certain score. The overall index is the sum of all scores and may range from 0 to 105, with 0 being no disease activity. The chronic morbidity at one year and at last follow up was

assessed using the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI).[16] The SDI consists of 41 items in 12 different domains, and it measures irreversible damage because each item is given a score when present for at least 6 months continuously. The total SDI score can range from 0 to 47 with 0 being no chronic damage. The SDI has recently been applied to childhood-onset SLE patients and found to have face, content and construct validity.[17] The project was approved by various Cluster Ethics and Research Committees of Hospital Authority.

Statistical analysis

The incidence of lupus nephritis was estimated by dividing the number of new cases by the estimated childhood population aged 0-18 years (as person-years of the at-risk population, obtained from Census and Statistics Department of Hong Kong Government) over the period of interest. The average incidences of lupus nephritis were calculated for each 3-year period from 1992-1994, 1995-1997, 1998-2000, 2001-2003 to show the changing trend of incidence over the past decade.

Summary statistics of all data were presented as mean$\pm$SD or range or frequency distribution. Survival data were presented as Kaplan-Meier survival curves. Differences between subgroups were tested for statistical significance by log-rank tests. Multiple logistic analysis of the risk factors for death/ESRF was performed using the Cox proportional hazard model. SPSS version 10.0 was used for statistical analysis.

Results

Our search identified 128 children with SLE nephritis within this 14-year period. They were all Chinese children. There were 120 girls and 8 boys with age at diagnosis ranging from 3.6 to 18.6 years (mean$\pm$SD 11.9$\pm$2.8 years). The age and sex distributions

are shown in Table 1. For each 3-year period of 1992-1994, 1995-1997, 1998-2000, and 2001-2003, there were 21, 22, 33 and 40 new cases of lupus nephritis respectively, while the total person-years of risk were 4 506 455, 4 629 956, 4 553 407, and 4 315 426 respectively. Thus the incidence of lupus nephritis were estimated to be 0.47, 0.48, 0.72, and 0.93 per 100 000 person-years for the above time periods. During the study period from 1990 to 2003, 1157 renal biopsies were performed in children aged 18 years or below.

Their presentations mainly fell into two patterns. Sixty-five patients (50.8%) had multisystemic symptoms of prolonged fever, polyarthritis and skin rash while renal involvements were indicated by urinary abnormalities only. In 51 patients (40%), the presence of nephrotic or nephritic features brought them to medical attention before the diagnosis of SLE. Other rare presenting features were immune thrombocytopenic purpura (2 patients), autoimmune haemolytic anemia (2 patients), pANCA-positive crescentic glomerulonephritis (1 patient), deep vein thrombosis (2 patient), renal arterial and venous thrombosis (1 patient), Raynaud's phenomenon (1 patient), intestinal vasculitis with intestinal bleeding, abdominal pain and ascites (1 patient). The patient with pANCA crescentic glomerulonephritis first presented at the age of 11 years with proteinuria, microhaematuria and renal impairment. She was positive for antinuclear antibody but negative for anti-dsDNA. She had strongly positive ANCA (perinuclear pattern) and anti-myeloperoxidase titre. Renal biopsy revealed fibrocellular crescents in all 6 glomeruli seen, with immunofluorescent staining showing weak IgG, C3 and C1a staining and negative IgA and IgM staining. She was treated with pulse methylprednisolone followed by oral prednisolone and cyclophopshamide/azathioprine maintenance for 3 years. There

was initial response but she relapsed at age of 15 years with full blown nephrotic syndrome, Coomb's positive haemolytic anaemia, and positive ANF and anti-dsDNA. Repeated renal biopsy showed diffuse proliferative glomerulonephritis with full house immunofluorescence staining.

Diagnosis of SLE was made usually within 3 months of onset of symptoms, but there was a delay of 3 to 12 months in 9 patients and of more than 1 year in 13 patients especially in those with the rare presenting features. Evidence of renal involvement was present at diagnosis in 92 patients, and developed within the first year of diagnosis in an additional 19 patients. However, in 17 patients, nephritis occurred more than one year after diagnosis of SLE.

Table 1 and 2 show the prevalence of various clinical features and significant laboratory tests within 3 months of SLE diagnosis in this cohort. Of special interest were 8 patients (6%) who had no detectable anti-dsDNA antibodies (sero-negative lupus). While anti-cardiolipin antibodies were prevalent (50.6% for IgG and 38.8% for IgM), lupus anti-coagulants were rare (positive in 17.4%), and clinical thrombosis occurred in only 4 patients. Three of these patients had typical SLE features including malar rash, leucopenia and thrombocytopenia, haematuria and proteinuria, positive ANF and anti-dsDNA and they developed deep vein thrombosis over the lower limbs 8 months before (1), at diagnosis (1) and 5 years after SLE diagnosis (1). They all had positive anticardiolipin and lupus anticoagulatnt antibodies. The fourth patient presented with polyarthritis, pleural effusion, Coomb's positive haemolytic anaemia, thrombocytopenia and gross haematuria. Ultrasound scan and Doppler revealed right kidney enlargement and artery and vein thrombosis. Her renal biopsy also yielded necrotic renal tissue

suggestive of infarction. She also had positive anti-dsDNA and lupus anticoagulant antibodies.

TTP was evident at SLE diagnosis in 4 patients. All of them had systemic SLE features, blood and renal involvement and positive ANF and anti-dsDNA antibodies. TTP was diagnosed in these patients because of the features of micro-angiopathic haemolytic anaemia on peripheral smear examination, thrombocytopenia and renal impairment. The renal biopsy also showed fibrin thrombi in some arterioles in addition to diffuse proliferative glomerulonephritis and full house immunoflurescence staining.

Table 4 shows that Class IV nephritis was the most common renal pathology, followed by Class III, V and II. There was a general trend that Class IV and V nephritis were associated with more severe renal manifestations with nephrotic syndrome or renal impairment. However, a significant proportion of patients with urinary abnormalities (38.9%) or those with normal eGFR and non-nephrotic-range proteinuria (28.6%) also had Class IV nephritis on initial biopsy. If patients with these renal manifestations were not subjected to renal biopsy, 15-30% of Class IV nephritis would have been missed.

Table 5 shows the variety of induction treatment that patients with different renal pathologies had received, and Table 6 shows their renal status at one year, relapses, need for additional treatment, and outcome at last follow up. All of the cases ending in death or end-stage renal failure (ESRF) occurred in Class IV patients. In the Class IV patients, those treated with prednisolone alone or prednisolone plus POCYC had a greater need for additional therapies and more severe renal sequalae (ESRF or impaired eGFR) while patients treated with IVCYC had good control of nephritis but more deaths which were related to treatment.

The duration of follow up ranged from 1 to 16.5 years with a median of 5.3 years (mean ± SD 5.76±3.61 years). Twenty-four patients were followed up for 10 or more years. Five (3.9%) patients died. One patient with Class IV nephritis was treated with prednisolone alone in the earlier years. She had poorly controlled nephritis despite subsequent addition of POCYC. She died with multiorgan failure in a lupus flare 2.6 years after diagnosis. One patient had Class IV nephritis which was well controlled after IVCYC but at 3.1 years from diagnosis he died suddenly due to myocarditis and cardiac tamponade during an acute flare. There were two deaths from infection. Both had Class IV nephritis treated with IVCYC regime. One died of tuberculous meningoencephalitis at 5.3 years and the second died of septicaemic shock at 9.8 years after diagnosis. Both had massive proteinuria though normal eGFR at the time of death. The fifth patient initially had Class V nephritis but subsequently developed crescentic Class IV nephritis despite POCYC induction. She had renal failure with eGFR 15 ml/min/1.73 m^2 at 5.5 years after diagnosis, when she opted for haematopoietic stem cell transplantation. However she died of cyclophosphamide-related cardiomyopathy during the conditioning phase.

Overall the patient survival rates at 5-years, 10-years and 15-years from diagnosis of SLE were 95.3%, 91.8% and 91.8% respectively. The 5-years, 10-years and 15-years renal survival rates (survival without ESRF) were 94.1%, 87.4% and 81.7% respectively. For Class IV nephritis patients, the 5-years, 10-years and 15-years renal survival rates were 91.5%, 82.3% and 76% respectively. There were no statistical differences in renal survival rates between different WHO classes of the initial biopsy (Figure). Analysis with the Cox proportional hazard model was performed with the outcome of death/ESRF and prognostic variables including sex, age at nephritis, persistent hypertension, Up/c and

eGFR at presentation, presence of Class IV nephritis, presence of membranous components in biopsy, induction therapy, Up/c, eGFR and SLEDAI at 1 year. It showed that only Up/c at presentation (B=0.615, SE= 0.28, p=0.028) and SLEDAI at 1 year (B=0.005, SE=0.002, p=0.03) were significant prognostic factors for death/ESRF.

Of the 123 survivors, 79 patients (64.2%) had no chronic organ damage at their last follow up. Twenty-seven patients (22%), eight patients (6.5%) and nine patients (7.3%) had a SDI of one, two and more than two respectively. Table 7 showed the organ-system distribution of SDI scores. The commonest organ damages occurred in renal, musculoskeletal systems and the eyes. ESRF occurred in 3 survivors (in addition, one death case also had ESRF). Two patients had renal impairment with eGFR<50 ml/min/1.73m^2, and 16 had nephrotic-range proteinuria. Nine patients (7.3%) developed avascular necrosis (8 had AVN of both femoral heads and one had AVN of talus). Cataracts were detected in 17 patients though all were partial (13.8%). Significant neurological sequalae and osteoporosis with fractures each occurred in only 1-2% of the survivors. Table 8 showed the infectious complications reported in our patients. Although infections were infrequent with only 53 episodes reported in 810 patient-years of follow-up (giving an incidence of 0.65 episodes per 10 patient-years), some infections were life-threatening and accounted for two deaths in our cohort.

Discussion

This study provided us with useful information on the epidemiology, clinical features, clinicopathologic correlation, treatment and outcome of an unselected cohort of SLE nephritis in Chinese children. We believe that this is representative of the local Chinese population because it involved a good sized sample of 128 children collected

over a 14-year period. The participating units included all hospitals that together provided more that 90% of both secondary and tertiary care to children in Hong Kong, thus avoiding selection bias commonly encountered in previous reports from tertiary centres.

In this Chinese cohort lupus nephritis occurred before 10 years old in 23% (rare before 5 years), and between 10 and 15 years in 70%. This was in agreement with the data of 556 children in the Pediatric Rheumatology International Trial Organization (PRINTO) which showed that 23% of childhood SLE had onset before 10 years.[3] Our cohort had a female to male ratio (F:M) of 2:1 before 5 years and 7.7:1 from 5 to 10 years. This was similar to previous reports by Cassidy et al (F:M of 4:3), King et al[18] (F:M 3:1) and the recent PRINTO data (F:M 5.3:1).[3] However, for patients above 10 years old, the F:M ratio of 20.8:1 in our cohort was much higher than the figures of 5:1 reported by Cassidy et al, or 5.8:1 by the PRINTO dataset[3] or 10:1 reported by King et al,[18]. This indicated the extreme rarity of male SLE in Chinese teenagers.

The overall incidence of SLE in all age-groups ranged from 1.9 to 8.7 per 100 000 population.[19] In the review by Cassidy and Ross, the incidence of SLE in children younger than 15 years were estimated to be 0.36 to 0.9 per 100,000 based on studies in 1970's.[20] We found an incidence of SLE nephritis in Chinese children ranging from 0.47 to 0.93 per 100 000 person-years. However these figures are not directly comparable as SLE nephritis is only a subset of all SLE patients. Another interesting finding in the present study was that the incidence had doubled from 1992 to 2003. This could be due to better recognition and documentation of renal involvement in SLE children, or it could be a genuine increase in the incidence of SLE nephritis in the Chinese population.

Roughly the same proportions presented with either the typical multi-system features of SLE (with nephritis indicated by urinary abnormalities only), or full blown nephrotic or nephritic features. Correlation with biopsy findings reiterated the general concept that the clinical presentations could not always predict WHO histopathologic classes. Hence renal biopsy should form part of the assessment in deciding on therapy for patients with any renal involvement. If renal biopsy was not performed in the patients with only urinary abnormalities or in those with normal eGFR and non-nephrotic proteinuria, a significant proportion of Class IV nephritis may have been missed. Although prior immunosuppressive treatment might have modified the clinical manifestations, it was not likely in our patients because most of them underwent renal biopsy at diagnosis of SLE before start of any therapy.

Since this was a territory-wide cohort, our review gave a fair estimate of the prevalence of seronegative lupus (6%), concurrent TTP (3%), and antiphospholipid syndrome (3%) in childhood lupus nephritis. TTP is a recognised association of SLE. Brunner reviewed 35 patients with childhood-onset TTP and found that 17 (49%) subsequently received the diagnoses of definite or incipient SLE.[21] However, TTP was not included as a complication or association in several large series of childhood SLE.[5;13;22] The prevalence of anticardiolipin antibodies in adult patients with SLE ranged from 12-30%, and those of lupus anticoagulants were 15-34%. After 20 years of follow up, 50-70% of these patients developed into antiphospholipid syndrome.[23] Our data indicated a higher prevalence (30-50%) of anticardiolipin antibodies, but a lower percentage (3% of the cohort or 10% of those with positive anticardiolipin antibodies) developed into antiphospholipid syndrome with genuine thromboembolism. However this

may be an underestimate since more patients may develop thrombosis on further follow up.

The treatment recommendations for adult SLE nephritis were well founded on good quality randomized controlled trials.[24] In children, data from randomized clinical trials were nonexistent and treatment recommendations were extrapolated from adult studies or derived from past reports of case series. Though most investigators suggested steroid plus POCYC or IVCYC as the standard therapy for Class IV nephritis, some authors have reported good results with steroid plus AZA, and they could not demonstrate any difference between AZA and CYC therapy.[25-27] Although our data were retrospective and non-randomized, we observed that all patients who died or developed ESRF (except one death) had Class IV nephritis at onset of disease. Those patients who received steroid alone had the worst outcome. While patients treated with POCYC developed ESRF, those treated with IVCYC died of complications of therapy (infections and cyclophosphamide cardiomyopathy). This was not observed in a report of adult Chinese SLE patients in which POCYC was found to be more effective but more toxic than IVCYC regimes.[28] Multivariate analysis, however, did not show any statistically significant differences in renal survival between different biopsy classes or different therapy, probably because of the small number of death/ESRF involved.

The prognosis of SLE nephritis in children has improved over the past 3 decades. Meislin et al in 1968 reported a 5-year patient and renal (alive without ESRF) survival rate of 43%.[4] In the 1990's, the 5-year patient and renal survival reported for SLE nephritis were 78% and 56% by McCurdy et al,[29] or 82.8% and 44.4% by Baqi et al.[26] Recent publication by Hagelberg in 2002 reported 5-, 10- and 15-year patient

survival rates to be 97%, 95% and 90% respectively.[25] In our study, the patient survival rates were 95.3% at 5 years and 91.8% at 10 years, while the renal survival rates 94.1% at 5-year and 87.4% at 10-years respectively. These figures were comparable to those reported by Hagelberg et al[25], Emre et al,[30], and Bogdanovic et al.[31]

Our series also had similar 5-year patient and renal survival rates when compared to the report by Yang et al from Taiwan in 1994 (95.3% and 91.8% in our series versus 93.1% and 91.1% reported by Yang respectively).[13] However our Class IV nephritis patients had better survival than their patients (91.5% versus 82% at 5-years). We also had longer follow-up data at 10 and 15 years. Understandably there was a gap of 10 years between the two reports, and our series included unselected patients of all severity while their patients were from a tertiary referral centre. When compared with adult Chinese patients, our series had slightly better outcome. Mok et al in 1999 analysed the outcome of adult Chinese SLE nephritis patients from the same community as ours. They reported patient survival rates of 98.8%, 94.4% and 94.4% at 5-, 10- and 15-years respectively, while the renal survival rates were 92.1%, 81.2% and 75.2% at 5-, 10-, and 15-years respectively. For Class IV nephritis adults, the renal survival rates were 89.1%, 71.1% and 61.4% at 5-, 10- and 15-years respectively.[10]

Data on chronic morbidity of SLE nephritis children were scarce in the literature, especially using standardized scoring systems such as the SDI. Our study showed that at the last follow up, 13.8% of survivors had two or more SDI. This percentage was much lower than the incidence of 51% of patients having an SDI of >2 in the report by Miettunen et al.[32] Compared with their series, our patients also had less chronic morbidity in the neuropsychiatric, cardiovascular or peripheral vascular systems.

In summary we described a representative cohort of Chinese children with SLE nephritis in Hong Kong. When compared with previous reports, SLE nephritis was rare in Chinese boys especially in teenage years. About half presented as multisystem disease and half presented with predominantly renal manifestations. On initial renal biopsy, 70% of patients had Class III and IV nephritis. Our experience supported the practice to perform renal biopsy on all SLE patients with evidence of nephritis. Though it was believed that non-Caucasian patients had worse prognosis, our series of Chinese children had good medium term survival similar to previous reports in the Caucasian population. Nevertheless death occurred due to lupus flare or infections, which reflected a delicate balance between adequate immunosuppression and overtreatment. Lastly we described chronic organ damage in our patients (as the standardized SDI), which was less common in our series than other reports. However renal damage and avascular necrosis of both hips were common long-term complications in our patients.

Acknowledgement:

We would like to thank the chiefs-of-service of all paediatric departments in Hong Kong Hospital Authority for their support and their approval for us to review the clinical data of the patients in their departments.

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Table 1. Age and sex distribution of 128 children with lupus nephritis

Age group	Female	Male	Total	Female: male ratio
0-4.99 years	2	1	3 (2.3%)	2.0 :1
5-9.99 years	23	3	26 (20.3%)	7.7 : 1
10-14.99 years	83	4	87 (70.0%)	20.8 :1
15-18.99 years	12	0	12 (9.4%)	NA

NA not assessable

Table 2: Clinical features in 128 Chinese children with SLE nephritis at the time of initial diagnosis.

Clinical features at diagnosis	No. present / No. recorded	Prevalence (%)
Systemic symptoms		
Prolonged fever	71/128	55.5
Malar rash	59/126	46.8
Polyarthritis	57/128	44.5
Skin vasculitis	35/122	28.7
Lymphadenopathy	22/123	17.9
Oral ulcers	22/125	17.6
Pericardial effusions	21/125	16.8
Photosensitivity	18/123	14.6
Alopecia	15/124	12.1
Discoid lupus	12/124	9.7
Seizures	12/127	9.4
Pleural effusion	11/126	8.7
Livedo reticularis	6/118	5.1
Raynaud's phenomenon	4/121	3.3
Skin ulcers	4/122	3.3
Psychosis	3/127	2.4
Phlebitis	1/122	0.8
Renal symptoms:		
Haematuria microscopic	101/126	80.2
Oedema	69/128	53.9
Hypertension	41/128	32.0
Urine casts	22/70	31.4
Haematuria gross	13/126	10.3

Table 3: Selected laboratory findings in 128 Chinese children with SLE nephritis at the time of initial diagnosis.

Laboratory features at diagnosis	No. present / no. tested	Prevalence (%)
Haematology tests		
Direct Coomb's test positive	74/124	59.7
Hb <10 g/dL	75/128	58.6
Lymphocytes <1.2 x 10^9/L	56/126	44.4
Leukocytes <4.0 x 10^9/L	52/127	40.9
Platelet count <100 x 10^9/L	42/126	33.3
Serological tests		
ANA positive	128/128	100
Anti-dsDNA positive	120/128	93.8
C3 complement < 0.75 g/L	119/128	93
C4 complement < 0.14 g/L	103/117	88
Anti-cardiolipin antibody (IgG) positive (>15 GPLU/mL)	42/83	50.6
Anti-*ro* antibody positive	41/88	46.6
Anti-cardiolipin antibody (IgM) positive (>13 MPLU/mL)	26/67	38.8
Lupus anticoagulant positive	8/46	17.4
Anti-*la* antibody positive	7/86	8.1
Anti-*sm* antibody positive	7/88	8

Abbreviations: Hb Haemoglobin level; ANA Antinuclear antibodies; Anti-dsDNA Antibody to double strand DNA

Table 4: Correlation of renal histopathology with clinical and laboratory features in 128 Chinese children with SLE nephritis

		Presenting clinical syndromes			Normal eGFR		eGFR < 90		eGFR <30
WHO Class	No. in each category	Urinary abnormalities	Nephrotic syndrome	Nephritic syndrome	Up/c < 2.0	Up/c >2.0	Up/c < 2.0	Up/c >2.0	
II	13 (10.2%)	11 (20.4%)	2 (4%)		9 (25.7%)	4 (6.5%)			
III	22 (17.2%)	14 (25.9)	4 (8%)	4 (16.7%)	8 (22.9%)	10 (16.1%)	2 (25%)	2 (10%)	
IV	69 (53.9%)	21 (38.9%)	30 (60%)	18 (75%)	10 (28.6%)	34 (54.8%)	6 (75%)	16 (80%)	3 (100%)
V	13 (10.2%)	1 (1.9%)	11 (22%)	1 (4.2%)	1 (2.9%)	11 (17.7%)		1 (5%)	
no/ in-adequate biopsy	11(8.6%)	7 (13.0%)	3 (6%)	1 (4.2%)	7 (20.0%)	3 (4.8%)		1 (5%)	
Total	128 (100%)	54 (100%)	50 (100%)	24 (100%)	35 (100%)	62 (100%)	8 (100%)	20 (100%)	3 (100%)

Abbreviations: Up/c urine protein to creatinine ratio in mg/mg; eGFR glomerular filtration rate in ml/min/1.73m^2 as estimated by Schwartz formula

Table 5: Initial induction treatment given to 128 Chinese children with SLE nephritis

WHO Class		Induction treatment given					
	No. in each category	Group 1 : Pred only	Group 2 : Pred+ AZA	Group 3: Pred+ POCYC	Group 4 : Pred+ IVCYC	Group 5 : Pred+ MMF	Group 6 : Pred+ CSA
II	13	9	1	3			
III	22	4	6	7	5[a]		
IV	69	14	6	25[b]	21	2[c]	1
V	13	3	1	4[d]	1	2	2
no/in-adequate biopsy	11	5	4[e]	1		1	
Total	128	35	18	40	27	5	3

Notes:

[a]one patient also received plasmapheresis for TTP

[b]one patient also received plasmapheresis, IVIg, IVCYC for one dose for TTP

[c]one patient also received plasmapheresis, IVMP, IVCYC for one dose for TTP, then switched to MMF

[d]one patient also received CSA

[e]one patient also received IVIg for renal vein thrombosis

Abbreviations: AZA azathiorpine; CSA cyclosporine A; IVCYC intravenous cyclophosphamide; IVIg intravenous immunoglobulin; IVMP intravenous methylprednisolone; MMF mycophenolate mofetil; POCYC oral cyclophosphamide; TTP thrombotic thrombocytopenic purpura.

Table 6: Treatment responses and outcome in patients with different WHO nephritis classes

WHO Class	Class II (n=13)	Class III (n=22)	Class IV (n=69)	Class V (n=13)	no biopsy (n=11)	Total (n=128)
Complete remission at 1 year	8	13	48	6	8	83 (65%)
Partial remission at 1 year	4	9	19	6	2	40 (31%)
Non-response at 1 year	1	0	2	1	1	5 (4%)
Relapsers	7	8	29	4	4	52 (41%)
Need for higher level of therapy	9	5	22	4	6	46 (36%)
Up/c >0.2 but <2.0 at last follow up	3	3	13	3	1	23 (18%)
Up/c $\geq$2.0 at last follow up	2	4	6	2	2	16 (13%)
eGFR<90 at last follow up	1	0	8	1	1	11 (9%)
ESRF at last follow up or death	0	0	4*	0	0	4* (3%)
Death	0	0	4*	1**	0	5* (4%)

Note: *one death case also had ESRF; hence total number of bad outcome was 7 in Class IV nephritis and 8 in whole group. **This patient had transformed to Class IV nephritis, needed also plasmapheresis and haematopoietic stem cell transplant but died.

Abbreviations: Up/c urine protein to creatinine ratio in mg/mg; eGFR estimated glomerular filtration rate by Schwartz formula; ESRF endstage renal failure.

Table 7: Organ system distribution of SDI scores assessed at last follow-up in 44 patients with chronic organ damage.

	Scores in this organ system	percentage
Eye		
Cataract	12	15.4%
Optic atrophy	1	1.3%
Neurological		
Cognitive	3	3.8%
Cerebrovascular accidents	3	3.8%
Neuropathy	2	2.6%
Epilepsy	2	2.6%
Renal		
Up/c>2.0mg/mg	16	20.5%
eGFR<50%	2	2.6%
ESRF	9*	11.5%
Pulmonary		
Pulmonary fibrosis	1	1.3%
Cardiac	0	0.0%
Vascular		
Venous thrombosis	2	2.6%
Minor tissue loss of pulp space	1	1.3%
Gastrointestinal tract	0	0.0%
Musculoskeletal		
Osteoporosis with fracture	*3*	3.8%
Avascular necrosis (AVN)	17**	21.8%
Osteomyelitis	1	1.3%
Skin	2	2.6%
Gonad	1	1.3%
Diabetes	0	0.0%
Cancer	0	0.0%
Total scores	78	100.0%

Abbrev.: Up/c urine protein to creatinine ratio in mg/mg; eGFR GFR estimated by Schwartz formula; ESRF endstage renal failure.

Note: *3 patients with ESRF with SDI of 3 each. **8 patients had bilateral AVN of femoral heads with SDI of 2 each.

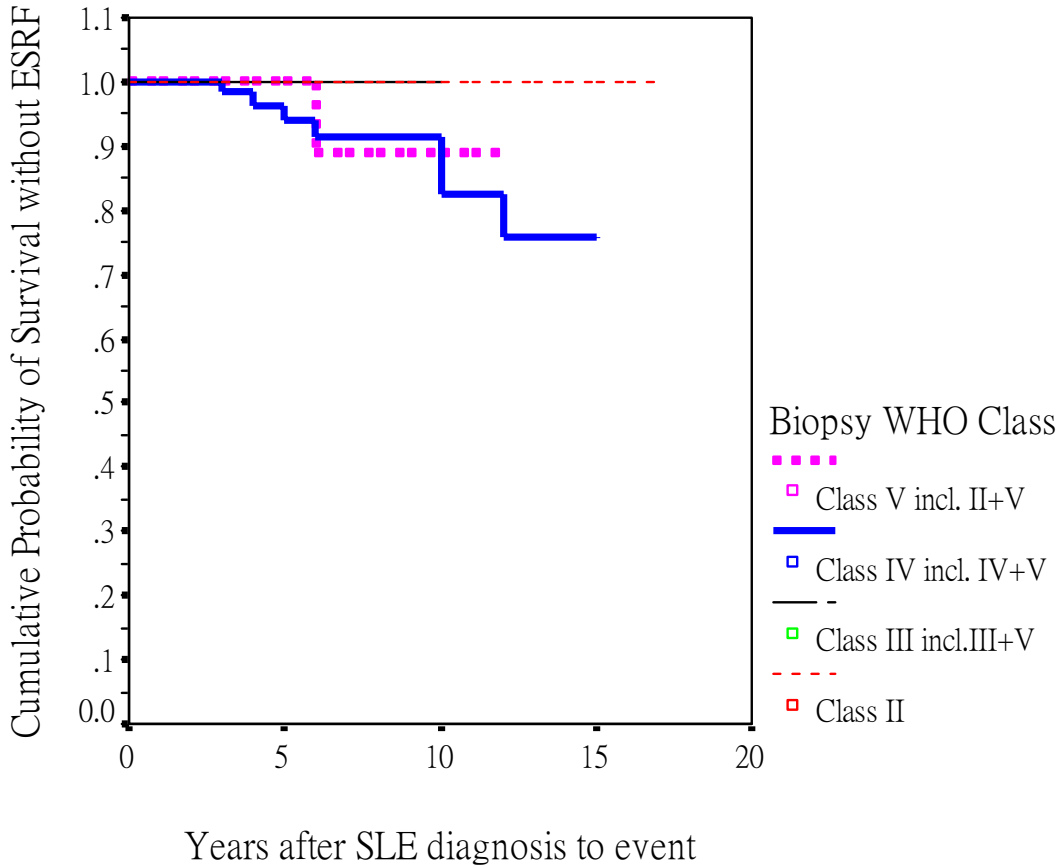
Table 8: Infectious complications in 128 Chinese children with SLE nephritis

Infectious complications	Patient-episodes
herpes zoster	26
Cellulitis	4
Septicemia (*Escherichia coli, Pseudomonas, Morganella & E.coli*)	3
Pneumocystis carinii pneumonia	3
Cytomegalovirus pneumonitis	3
herpes simplex gingivitis	2
urinary tract infections	2
Pneumonia (presumed bacterial)	2
Septicaemic shock (organism unknown)	1*
Tuberculous meningoencephalitis	1*
osteomyelitis (Salmonella sp.)	1
acute otitis media	1
breast abscess	1
candida endophthalmitis	1
viral meningoencephalitis	1
viral hepatitis	1
Total episodes	53

Note: *resulting in death of patient

Legend for figure:

Kaplan-Meier survival curves for renal survival of patients in each WHO Class



No. remaining					
	V	13	9	1	
	IV	69	40	17	3
	III	22	11	4	
	II	13	8	2	1