ORIGINAL ARTICLE

Systemic Lupus Erythematosus in Filipino Children: A 10-year Retrospective Analysis of Mortality, Morbidity and Survival

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ABSTRACT

Background. Systemic Lupus Erythematosus (SLE) in children has been estimated to account for 15 to 20% of all SLE cases worldwide. It was described to have more severe disease at presentation including renal, neuropsychiatric, and hematologic involvements; more disease activity over time, and a significantly higher risk of organ damage. Thus, considered a significant risk factor for mortality among adult SLE patients.

Objective. This is a retrospective cohort study aimed to determine the clinical profile, outcome, and survival of SLE among Filipino children.

Methods. All SLE patients, less than 19 years old, diagnosed in the pediatric department of a tertiary hospital from January 2008 to December 2017 were included in the study. Their medical charts were retrieved for data gathering. Demographics, and clinical disease characteristics were collected from admission and on subsequent follow ups. Lost to follow up patients were contacted for updates of their current clinical status.

Results. A total of 261 pediatric SLE patients were gathered. Average age at diagnosis is 14.5 years old (±2.7), with female to male ratio of 16:1. Symptoms starts at 3 months prior to consult (±2.1). Upon diagnosis, most of the patients have fever, malar rash, alopecia, oral ulcers, and proteinuria. Most common systemic organ involvement through time were mucocutaneous, hematologic, and renal. Steroids were the mainstay management for all patients, in which 95% started on oral Prednisone, while 71% needed IV Methylprednisolone in at least once during the disease course. Two patients received biologic treatment. Overall mortality rate was 14.9%, identified to be secondary to sepsis and/or SLE activity. Myocarditis, pleural effusion, and seizures were identified as significant risk factors for mortality. Survival rate at 1 year and 10 years were 92% and 79%, respectively.

Conclusion. SLE in Filipino children mostly presents with mucocutaneous symptoms. Presence of seizures, myocarditis, and pleural effusion at any time of the disease entails risk for mortality. SLE nephritis is a substantial cause of morbidity due to its chronicity. The survival rate of Filipino children with SLE is comparable with the data from other developing countries.

Keywords: systemic lupus erythematosus, SLE, pediatric SLE, survival analysis, clinical series, clinical profile

INTRODUCTION

SLE in children comprises 15-20% of the disease population, worldwide.[1-5] It is characterized by extremely variable disease presentation and an unpredictable clinical course as compared to adult SLE.[4] It has been reported having high severity at disease compared to later onset in adults.[5] Furthermore, a late recognition and diagnosis of childhood-onset SLE increases the risk for mortality.[6] Its occurrence worldwide is variable depending on factors such as access to care, referral patterns, and ethnic diversity.[1]

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The current global incidence of SLE in children ranges from 0.36 to 2.5 per 100,000 children and has a prevalence of 1.89 to 25.7 per 100,000.[4,7] They tend to have more severe disease at presentation, more disease activity over time, and a significantly higher risk of disease damage compared with their adult counterparts. Clinically, systemic manifestations such as renal, neuropsychiatric and hematologic involvements are more common in childhood-onset SLE, and significantly contributes to poor long-term outcome.[8-10] More to the predilected organ involvement and severity at the onset, pediatric SLE patients had longer disease duration, predisposed to more flare recurrences over time and subsequently more treatment-related adverse effects.[9] Severe organ involvement related to SLE itself and infection remain the main causes of early mortality.[8,10-12] Hersh et al. concluded in their study that childhood-onset SLE is a predictor of mortality among adult patients with SLE.[13]

In the last three decades, we have seen an imperative increase in the survival rate of SLE patients.[9] In a study done by Tektonidou and associates in 2016, they concluded that in high-income countries, the 5-year and 10-year survival estimates were 99% and 97% respectively.[14] This improvement of survival was attributed to a number of factors such as the early diagnosis of renal disease, better serological monitoring, more judicious use of corticosteroids and cytotoxic agents such as IV cyclophosphamide and azathioprine, availability and advancement of renal replacement therapies, and better management of associated complications like infection, hyperlipidemia and hypertension.[9,14] In addition, progress in several other areas of clinical medicine, including diagnostic imaging, intensive care services, dialysis, and transplantation and judicious antimicrobial therapy all contributes to the improved outcome and survival of SLE patients.[11] These results demonstrate that pediatric SLE increased their life expectancy but are now faced with new types of morbidity because of the sequelae of the disease and prolonged treatment.[12]

Factors attributed to the disparities in the incidence, severity, and outcomes of adults SLE patients are well characterized; women, minorities, those lacking medical insurance, and those with lower socioeconomic status are at increased risk for developing the disease and for poor outcomes.[15] Fewer studies have examined the interplay of the above-mentioned disparities among children with SLE. In a cohort study of Lupus in Minorities[16], it was noted that childhood-onset SLE had more active disease during the entire follow-up period as measured by the physician rating of disease activity. Increased SLE activity is likely to result in greater requirement of aggressive treatments to control disease, and in the longer term more disease damage. Furthermore, young adults with childhood-onset SLE were two times more likely to be living in poverty, which may represent an important negative prognostic factor for these patients. This was noted in other studies done in Brazil, Taiwan and Africa.[17-19] Although there have been few studies on survival patterns in Indian and Thai patients with SLE,[19,20] data on survival patterns of pediatric SLE is scarce in other Southeast Asian countries in international literature. In the Philippines, a study of Gulay and Dans in 2005 described the overall 5-year mortality rate of pediatric SLE at 11.5% and infection was its major cause (77%). Furthermore, it was stated that majority of patients came from low-income families, resulting to poor treatment compliance, adherence and follow-up.[12]

OBJECTIVES

In this current study, we retrospectively followed a cohort of pediatric SLE patients at a given study period; however, as the study was conducted retrospectively, selection bias and incompleteness of records were inevitable. We primarily aimed to determine the clinical profile, and outcome of pediatric SLE patients seen in a tertiary referral center for the period of 10 years. We also aimed to identify the risk factors for mortality and generate the survival rate among these patients. Furthermore, this study will serve as a baseline local data for future studies and clinical guideline developments in diagnosis, management, and follow-up monitoring strategies of pediatric SLE patients both locally and worldwide.

METHODS

This was a retrospective cohort study done at the pediatric rheumatology clinic of a tertiary referral center. All SLE patients under 19 years old who were diagnosed in the pediatric department from January 2008 to December 2017 were included in the study. Pediatric SLE patients who have syndromes overlapping with other rheumatologic conditions such as SLE with Juvenile Dermatomyositis, SLE with Juvenile Idiopathic Arthritis and mixed connective tissue diseases were excluded.

A review of the Pediatric Rheumatology Section's admission census logbooks and subsequent retrieval of medical records were done. Adult rheumatology OPD admission logbooks were likewise reviewed to determine the status of last follow up. Patients who were lost to follow up (no show for at least 6 months) were contacted for update of their current condition. This was done through short messaging services, Facebook messenger, and telephone calls, using the ethical board-approved verbal consent script. Data Collection Forms were used to gather data.

Patients' data were anonymized and encoded in an encrypted excel file, which was only accessed by the investigators. Confidentiality of records were ensured by using a coded data collection form. Data Governance system within the Department of Pediatrics and Section of Pediatric and Adult Rheumatology complied with the set guidelines by the Data Privacy Act of 2012.

The demographic factors such as sex, birth date, onset age, interval time from the onset of symptoms to diagnosis,

date of diagnosis, duration of follow up, and/or death were collected. The initial disease presentations based on history data such as those listed in the 1997 revised ACR and 2012 SLICC classification criteria as well as other subsequent signs and symptoms were recorded. The laboratory data collected at diagnosis were: evidence of hemolysis (hemoglobin <100g/L) with high reticulocyte count (>0.015), leukopenia (WBC <4000/mm^3), lymphopenia (lymphocyte count <1500/mm^3), thrombocytopenia (platelet <150 x10^9/L), proteinuria (3+ dipstick/ >500 mg/mm^3), cellular cast, elevated creatinine (>1 mg/dl), positive ANA (done in at least 1:80 dilution or by indirect immunofluorescence method), positive anti-dsDNA, anti-Smith antibody, low C3 (<80 mg/dl), positive Coomb's test, and positive Anti-phospholipid antibodies.

Therapeutic strategies and medications during the entire course of the illness were recorded such as pulse methylprednisolone, IV corticosteroids, oral corticosteroids, and other immunosuppressants such as IV cyclophosphamide, azathioprine, methotrexate, and biologics such as Rituximab as well as other supportive medications. Complications of both the disease and medications, and causes of death were collected and analyzed. The infection rate was calculated as the number of infected patients divided by all patients. End-stage renal disease was defined as the time when renal replacement therapy (dialysis) was initiated.

The clinical course of all patients was followed up until December 31, 2017, death, or lost to follow up. Improvement was defined as remission or low disease activity and not needing hospital admission for disease management. Patient who did not improve was defined as one who was admitted or needed hospital admission for management of active SLE by the end of the study period (December 31, 2017). Patients who died were identified, noting their length of follow-up at both of Pediatric Rheumatology or Adult Rheumatology OPD clinic. The main clinical or pathological process resulting in death was recorded as the primary cause of death. Survival was calculated from the date of diagnosis to December 31, 2017 or until death.

Outcome Measures

Primarily, this study determined the presenting clinical and laboratory features of pediatric SLE, the time of diagnosis, medications received, and complications encountered either due to disease itself or treatment-related at any time during the disease course. Secondly, the generation of 10-year survival rate of pediatric SLE and associated risk factors for mortality was done.

Statistical Analysis

All data were encoded in an encrypted master list excel file. Qualitative variables were represented by frequencies and analyzed using Fisher's exact test. Normally-distributed quantitative variables were presented as means and standard deviation. Quantitative variables which were non-normally distributed were presented as median and interquartile range and employed Mann Whitney U test. Encoding and analysis were done using SPSS software. Descriptive statistics was used to summarize clinical data for pediatric SLE patients. Data were analyzed using means and standard deviation, frequency counts and proportions. The mortality rate was defined as the number of deaths divided by the total number of patients who followed up. The survival probabilities were estimated using the Kaplan-Meier method. Association of clinical risk factors was determined employing logistic regression. Level of significance was set at 5% confidence interval.

RESULTS

Demographics and Disease Characteristics

Of the 272 pediatric SLE patients seen by the section of pediatric rheumatology over the study period from January 2008 to December 2017, a total of 261 were included. Eleven were excluded due to missing medical chart records and inaccessible patient contacts. All patients met the ACR or SLICC criteria for the diagnosis of SLE. One hundred ninety-five patients are still on active follow up at our institution, in which 113 (58%) were transitioned to Adult Rheumatology Clinic, while the remaining 82 patients (42%) are still under the Pediatric Rheumatology Clinic. Thirty patients were contacted to assess their current clinical status. Of these, only 12 responded. Nine patients are still alive and on follow up with their nearest private rheumatologist. Three patients died and the reported causes of death were claimed to be Pneumonia, SLE activity and GI bleeding, respectively (Figure 1).

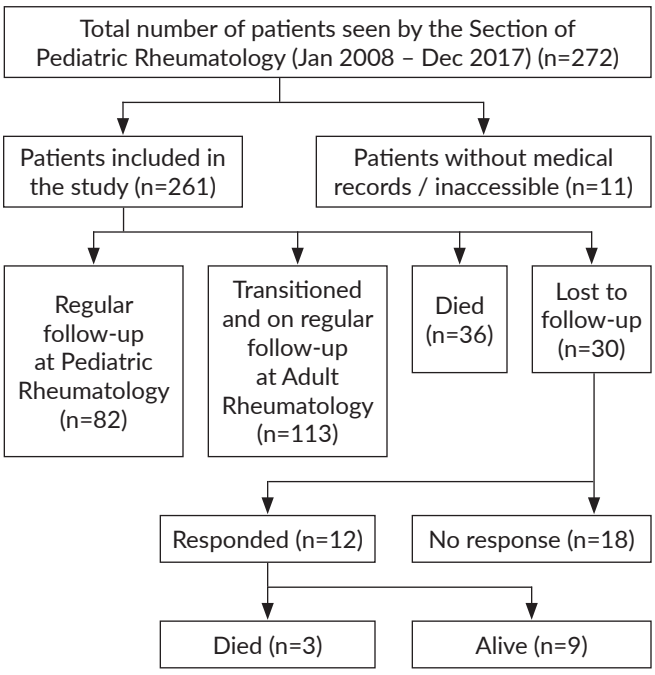

Figure 1. Study population distribution.

Table 1. Demographic characteristics of SLE patients seen in PGH, Jan 2008 – Dec 2017

Clinical Profile	
Age of Diagnosis, *(years) mean ± SD*	14.5 ± 2.7
Gender, *n (%)*	
Male	15 (5.8)
Female	246 (94.2)
Reported Onset of Symptoms prior to consult *(months), mean ± SD*	3.0 ± 2.1

The average age at diagnosis is 14.5 years old and are mostly female (94.2%) with female to male ratio of 16:1. The follow-up period ranged from 0.1 - 11.5 years. The mean onset of symptoms prior to consult is 3 months (±2.1) (Table 1).

Mucocutaneous manifestations are the most common reason for consult among pediatric SLE patients. These are malar rash (88.1%), alopecia (82%) and oral ulcers (78.5%). Almost 50% of patients reported fever as one of their initial manifestations. Serious or life-threatening initial symptoms such as seizures (34.5%), myocarditis (23.8%), acute renal failure (12.6%), and blurring or loss of vision (10.3%) are notably high among our patients (Table 2).

Table 3 shows that, 90.4% of patients had positive ANA tests while 56.7% had positive anti-dsDNA tests as major immunologic criteria for SLE diagnosis. Majority of the SLE patients had proteinuria (77.4%), red cellular cast (78.9%), and hemolytic anemia (61.3%) at the time of diagnosis (Table 3).

Furthermore, it was noted that kidney biopsy was only done in 8.7% of lupus nephritis patients and majority are of class IV lupus nephritis (50%).

Treatment and Disease Outcomes

Majority of pediatric SLE patients received glucocorticoid therapy, mainly Prednisone (95.4%), IV Hydrocortisone (12.6%), and Pulse Methylprednisolone therapy (71.3%). Most of our patients (91.2%) were also taking Hydroxychloroquine. In addition, 60.9% of the patients were given Naproxen as initial anti-inflammatory agent. Thirty-eight percent of patients received Cyclophosphamide infusion and 23% were given Mycophenolate mofetil as additional immunosuppressant. Other immunosuppressant such as Azathioprine was also given specifically to some patients (6.1%) with signs of persistent disease activity despite maximum steroid regimen or if with contraindication such as pregnancy. Biologic therapy, specifically Rituximab was instituted to 2 patients. Indications were SLE myelitis and persistent active SLE unresponsive to conventional non-biologic therapy.

Medications given for concomitant hypertension secondary to lupus nephritis, were mainly Enalapril (31.4%), Amlodipine (8.8%), Nifedipine (5.0%), and Losartan (1.9%). Table 4 shows systemic manifestations and complications among pediatric SLE patients during the entire course of the disease. Malar rash (91.6%), alopecia (87.4%), and nephritis (84.3%) are among the most common manifestations. Furthermore, cutaneous, renal, and hematologic organ involvements predominate in SLE disease in children (Table 4.1).

Table 4.2 presents the infections that were associated with the pediatric SLE patients during their entire disease course. Pneumonia in the immunocompromised host

Table 2. Initial clinical manifestations of pediatric SLE patients seen in PGH, Jan 2008 – Dec 2017

Clinical Manifestations	n=261 (%)
Mucocutaneous	
Malar Rash	230 (88.1)
Alopecia	214 (82.0)
Oral Ulcers	205 (78.5)
Photosensitivity / Photosensitive Rash	132 (50.6)
Discoid Rash	124 (47.5)
Maculopapular Rash	94 (36.0)
Vasculitic Rash	34 (13.0)
Musculoskeletal	
Synovitis	177 (67.8)
Joint Pains	42 (16.1)
Myalgia	3 (1.1)
Numbness of Hands and Feet	1 (0.4)
Serositis	
Pleural Effusion	116 (44.4)
Pericardial Effusion	59 (22.6)
Chest Pain	3 (1.1)
Difficulty Breathing	2 (0.8)
Neuropsychiatric	
Seizures	90 (34.5)
Behavioral Changes	26 (10.0)
Headache	8 (3.1)
Cardiac	
Myocarditis	62 (23.8)
Renal	
Edema	45 (17.2)
Acute Renal Failure	33 (12.6)
Hypertension	4 (1.5)
Ophthalmologic	
Retinopathy	25 (9.6)
Blurring Vision	2 (0.8)
Gastrointestinal	
Hepatitis	19 (7.3)
Melena	1 (0.4)
Hormonal	
Amenorrhea	14 (5.4)
Abnormal uterine bleeding	2 (0.8)
Prolonged Menses	1 (0.4)
Hematologic	
Pallor	11 (4.2)
Vascular	
Raynaud's Phenomenon	4 (1.5)
Fever	122 (46.7)

Table 3. Laboratory findings at diagnosis of SLE patients seen in PGH, Jan 2008 – Dec 2017

Laboratory Findings at Diagnosis	n=261 (%)
Urine Red Cell Cast	206 (78.9)
Proteinuria	202 (77.4)
Hemolytic Anemia	160 (61.3)
Leukopenia	111 (42.5)
Thrombocytopenia	94 (36.0)
Increased Creatinine	86 (33.0)
Lymphopenia	75 (28.7)
ANA +	236 (90.4)
Anti-dsDNA+	148 (56.7)
Low C3	127 (48.7)
Direct Coombs Test +	83 (31.8)

(14.8%) is the most common followed by Urinary Tract Infection (12.8%), and soft tissue abscess (11.6%). (Table 4.2)

A total of 39 deaths (14.9%, 95% CI 11.1% to 19.8%) occurred during the study period, three of which were known upon contacting lost to follow up patients. The causes of death were septic shock (16), SLE activity, myocarditis (9), SLE nephritis (7), SLE cerebritis, status epilepticus and diffuse encephalopathy (4), disseminated Intravascular Coagulopathy (1), massive GI bleeding (1), and Dengue shock syndrome (1). Isolated bacterial growths from those in septic shock were Pseudomonas aeruginosa (3), Burkholderia cepacia (2), Acinetobacter baumanii (2), and Methicillin-resistant Staphylococcus aureus (2). Although 78.5% were alive, 0.8% did not improve and were currently being

Table 4.1. Systemic manifestation and complications in the course of pediatric SLE seen in PGH, Jan 2008 – Dec 2017

Systemic Manifestations and Complications	n=261 (%)
Mucocutaneous	
Acute Malar Rash	239 (91.6)
Alopecia	228 (87.4)
Oral Ulcer	214 (82.0)
Discoid Rash	144 (55.2)
Photosensitive Rash	140 (53.6)
Maculopapular Rash	107 (41.0)
Vasculitic Rash	42 (16.1)
Hypertrophic Rash	9 (3.4)
Discoid rash with scarring	5 (1.9)
Bullous Rash	5 (1.9)
Panniculitis	4 (1.5)
Chillblain	1 (0.4)
Renal	
LN Class III	6 (2.3)
LN Class IV	9 (3.4)
LN Class V	3 (1.1)
LN unclassified	202 (77.4)
ARF	47 (18.0)
ESRD	18 (6.9)
Hematologic	
Hemolytic Anemia	195 (74.7)
Thrombocytopenia	107 (41.0)
Leukopenia	124 (47.5)
Lymphopenia	89 (34.1)
Disseminated Intravascular Coagulopathy	2 (0.8)
Musculoskeletal	
Synovitis	187 (71.6)
Avascular Necrosis	5 (1.9)
Muscle Atrophy	2 (0.8)
Persistent Myalgia	2 (0.8)
Neurologic	
Seizure	108 (41.4)
Behavioral Changes	35 (13.4)
Headache	12 (4.6)
Myelitis	2 (0.8)
Serositis	
Pleural Effusion	128 (49.0)
Pericardial Effusion	73 (28.0)
Ascites	17 (6.5)
Cardiovascular	
Myocarditis	75 (28.7)
Hypertension	22 (8.4)
Raynaud's Phenomenon	3 (1.1)
Aortic Dilatation	1 (0.4)
Vasculitis with Gangrene	1 (0.4)
Ophthalmologic	
Retinopathy	32 (12.3)
Uveitis	5 (1.9)
Cataract	2 (0.8)
Gastrointestinal	
Hepatitis	20 (7.7)
Enteritis	2 (0.8)
Pancreatitis	2 (0.8)
Splenomegaly	1 (0.4)
GI Bleeding	1 (0.4)
Pulmonary	
Pulmonary Hemorrhage	4 (1.5)
Interstitial Lung Disease	2 (0.8)
Pulmonary Hypertension	1 (0.4)
Others	
Thyroiditis	3 (1.1)
Overlap with Acute Myelogenous Leukemia	1 (0.4)
Macrophage Activation Syndrome	1 (0.4)

Table 4.2. Infectious complications among pediatric SLE patients seen in PGH, Jan 2008 – Dec 2017

Infectious Complications	n=165 (%)
Pneumonia	37 (14.8)
Urinary Tract Infection	32 (12.8)
Soft tissue abscess	29 (11.6)
Tuberculosis	28 (11.2)
Oral Candidiasis	17 (6.8)
Sepsis	12 (4.8)
Varicella	3 (0.4)
Otitis media	3 (1.2)
Dengue Hemorrhagic Fever	1 (0.4)
Amoebiasis	1 (0.4)
Ascariasis	1 (0.4)
Meningitis	1 (0.4)

admitted for active SLE at the time of study. Majority of the improved patients (95.5%) were still on regular follow up at the outpatient clinic of both pediatric and adult rheumatology services while 4.5% transferred to private rheumatologists in their respective provinces (7.3%) (Table 5).

Figure 2 shows that the mean survival time for pediatric SLE patients is 9.3 years at 95% CI (8.5-9.7 years). In addition, survival analysis revealed that after 0.1 month (3 days) from the time of diagnosis, the survival proportion is at highest (97.7%). By 1 year after diagnosis (12.1 months), survival proportion is at 91.9%, and 90.6% after 1.5 years (17.3 months). Moreover, it is shown that the survival curve did not drop to 0.50 or below median time, and lowest is above 75% survival probability. Therefore, survival probability is maintained high at around 81% after 5 years (60 months). The longest survival time which is at 73.4 months still show a high proportion of survival at 79% (Figure 2).

Table 5. Clinical outcome of pediatric SLE patients in PGH, Jan 2008 – Dec 2017

Clinical Outcome	n=261 (%)
Alive	204 (78.5)
Improved	202 (99.0)
Hospital OPD follow-up	193 (95.5)
Under private rheumatologist	9 (4.5)
Not Improved	2 (1.0)
Died	39 (14.9)
SLE activity	22 (56.4)
Myocarditis	9 (41.0)
Nephritis	7 (31.8)
Neuropsychiatric	4 (18.2)
Massive Bleeding / Disseminated Intravascular Coagulopathy	2 (9.1)
Infection	17 (43.6)
Clinical sepsis	6 (35.3)
Pseudomonas aeruginosa	3 (17.6)
Burkholderia cepacian	2 (11.8)
Acinetobacter baumanii	2 (11.8)
Methicillin-resistant *Staphylococcus aureus*	2 (11.8)
Dengue shock syndrome	1 (5.9)
Pneumonia	1 (5.9)
No response (unknown outcome)	18 (6.9)

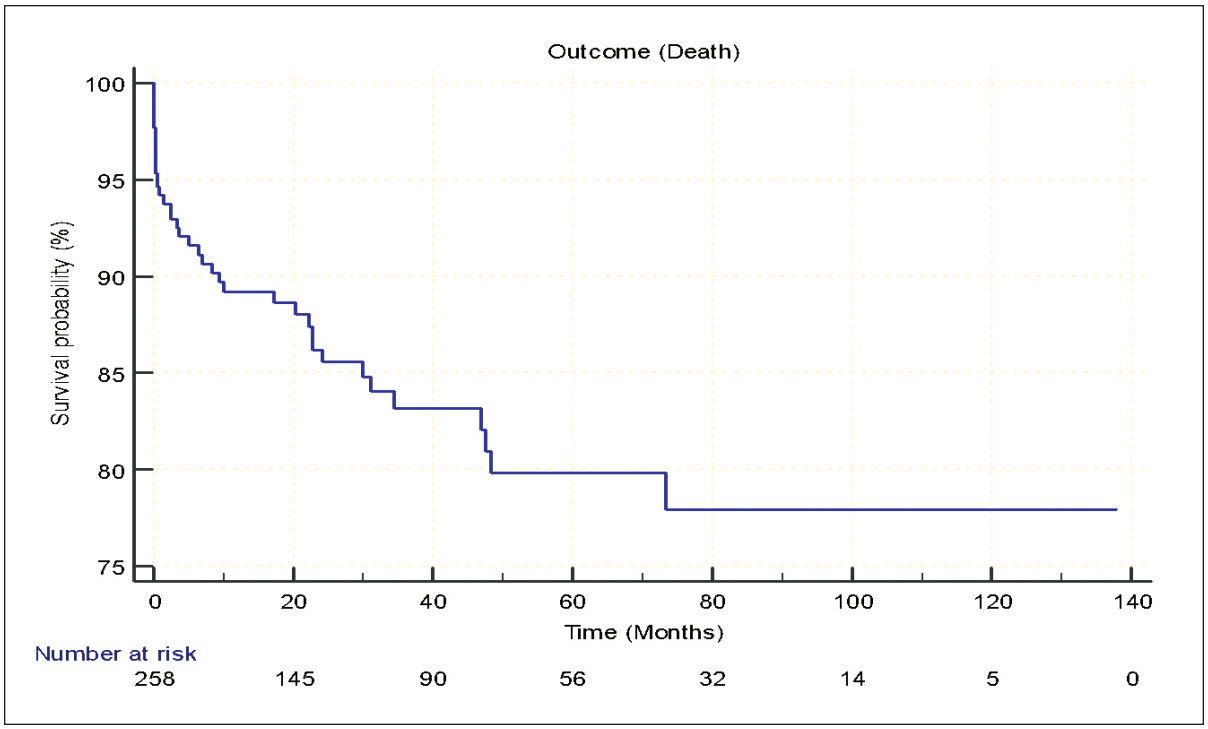

Figure 2. Kaplan Meier survival rate analysis.

Table 6.1. Risk factors associated with mortality in pediatric SLE seen at PGH, Jan 2008 – Dec 2017

	OR	95% CI for OR	p value
Age	0.90	0.83 to 0.99	0.0224
Gender	1.44	0.39 to 5.35	0.5882[ns]
Reported Onset of Symptoms	0.84	0.68 to 1.03	0.0951[ns]
Age of Diagnosis	0.89	0.79 to 1.00	0.0440

Table 6.2. Clinical and laboratory mortality risk factors in pediatric SLE seen in PGH, Jan 2008 – Dec 2017

Clinical Manifestations	OR	95% CI for OR	p value
Joint pains	0.74	0.27 to 2.00	0.5479
Vasculitic rash	0.73	0.24 to 2.21	0.5786
Alopecia	2.11	0.71 to 6.23	0.1803
Fever	1.01	0.39 to 2.58	0.9912
Malar rash	0.90	0.32 to 2.51	0.8436
Maculopapular rash	1.28	0.64 to 2.57	0.4805
Photosensitivity / Photosensitive rash	1.17	0.59 to 2.31	0.6579
Discoid rash	1.35	0.68 to 2.67	0.3913
Oral ulcers	3.76	1.11 to 12.72	0.0329*
Synovitis	0.72	0.36 to 1.46	0.3642
Pleural effusion	6.25	2.74 to 14.22	0.0001*
Edema	-	-	0.9976
Seizures	9.00	4.04 to 20.06	0.0001*
Pericardial effusion	2.20	1.06 to 4.58	0.0344*
Acute renal failure	3.57	1.57 to 8.15	0.0025*
Retinopathy	0.76	0.22 to 2.66	0.6652
Behavioral changes	1.41	0.50 to 3.99	0.5197
Myocarditis	5.89	2.87 to 12.09	0.0001*
Laboratory Findings	**OR**	**95% CI for OR**	**p value**
Proteinuria	1.72	0.69 to 4.34	0.2470
Cellular cast	1.98	0.73 to 5.32	0.1774
Hemolytic anemia	3.36	1.42 to 7.93	0.0058*
Thrombocytopenia	1.86	0.94 to 3.70	0.0760
Increased creatinine	1.71	0.86 to 3.43	0.1282
Leukopenia	2.48	1.23 to 5.00	0.0108*
Lymphopenia	2.82	1.40 to 5.65	0.0036*
ANA+	0.91	0.30 to 2.82	0.8761
Low C3	1.44	0.73 to 2.86	0.2953
Anti-dsDNA+	0.99	0.50 to 1.96	0.9679
Coombs Test+	1.83	0.91 to 3.66	0.0895
Kidney Biopsy LN	-	-	0.9979

**-significant (p<0.05)*

Table 6.1 shows that gender (p = .5882), and onset of symptoms (p = .0951) have no significant effect on mortality. On the other hand, the age at diagnosis turns out to be significant (p = 0.0440) and an odds ratio of 0.89 suggest that the younger the patient, the probability of death is higher (Table 6.1).

Table 6.1 shows the clinical manifestations that may lead to a higher chance of mortality, specifically, occurrence of seizures (p = .0001), pleural effusion (p = .0001), and myocarditis (p = 0.001) are significant risk factors to death. Specifically, denotes that those who developed seizures has 6.0 times higher likelihood for mortality. Similarly, those who developed pleural effusion and myocarditis are 5 times higher risk for mortality as compared to those who do not have. Furthermore, data shows that patients who have hemolytic anemia (p = .0058), leukopenia (p = .0108) or lymphopenia (p = .0036) are significantly associated to mortality. Specifically, those with clinical findings of hemolytic anemia has increased risk of 2.65, and lymphopenia at 2.34 higher risk for mortality (Table 6.2).

DISCUSSION

We have described the demographic features, presenting features, associated laboratory and clinical manifestations of SLE in Filipino children diagnosed and followed up for 10 years. In addition, risk factors for mortality and survival rate were likewise determined. Study results were compared to related local studies and from those reported from other countries as well.

In this study, the mean age of onset of SLE among Filipino pediatric patients is at 14 years (14.5 ±2.7) with the youngest reported patient at 5 years old. Female to male ratio is 16:1. This is comparable to other similar pediatric SLE studies done locally and worldwide.[12,21,22] Majority of patients are females across all studies with slight proportion differences when compared to age,[8] signifying the role of hormonal influence in the pathophysiology of the disease. We encountered mostly female (94.3%) patients with fewer reported males (5.7%).

Diagnosis of SLE was made after around 3 months (3.0 ±2.1) from the onset of initial symptoms. This may be attributed to multiple factors such as complexity of the evolving disease in pediatric age group, presence of non-specific constitutional signs and symptoms, or by the timing of the onset of symptoms as it may present in evolving manner. Moreover, it is fact that systemic rheumatic diseases have several overlapping features with multitude of systemic diseases such as malignancy and infections making it difficult to make a diagnosis at the onset.

Almost all studies uniformly reported mucocutaneous involvement as the most common feature of SLE at the onset.[12,21,23] This is in the form of malar rash, photosensitivity, oral ulcers, and alopecia, findings consistent with our cohort of patients. Discoid rash which was considered to be a rare manifestation upon onset[24] was noted to be higher in almost half of our patients (47.5%). Musculoskeletal symptoms upon onset of SLE was reported in 70-80% of SLE patients. Synovitis is one of its most common initial manifestations and was likewise noted to be 67.8% among our study patients. Renal involvement is a significant factor contributing to morbidity and mortality of pediatric SLE patients. It occurs at 50-75% of all cases and 90% are estimated to progress to chronic renal disease in 2 years.[25] In this study, we noted 12.6% of patients presented as acute renal failure, 78.9% presented with laboratory findings of

red cell casts, and 77.4% with significant nephrotic range proteinuria. In the entire disease course, nephritis was noted in 79.3% of patients. Unfortunately, only 18% have underwent kidney biopsy with prominent findings of LN class IV. This was notably lower compared to the previous study done in 2007[12], wherein kidney biopsy rate was at 30%. This is mainly due to the limited resources that we have in our institution and the socioeconomic status of our patients.

Immunologic tests, primarily ANA positivity approached hundred in most of the related studies[18,26] done in other countries. Immunologic testing of almost all of our patients were done in our immunology laboratory with standardized testing technique. Due to the scarcity of resources, taking into consideration the clinical status of each patient, there are instances that we choose to limit testing to ANA alone, followed by anti-dsDNA and other immunologic tests as necessarily indicated, without compromising the timely standard treatment. In our study, we obtain an equally high ANA positive rate (90.4%), and anti-dsDNA positive in 56.7% despite some patients on oral immunosuppression prior to immunologic testing.

Despite the advances in diagnosis and management, complications attributable to SLE or its treatment continue to cause substantial morbidity and mortality.[9,11] Infection was still the leading complication, and cause of mortality among our patients. This was also comparable to almost all of outcome studies in SLE.[4,9,11,13,20] The common reported infections were Pseudomonas, Burkholderia, and Acinetobacter which are almost exclusively hospital-borne bacteria. Furthermore, major organ manifestations, particularly CNS and renal diseases, have long been identified as markers of poor prognosis.[21,27] Seizure was found to be associated with a poorer overall survival of SLE in a study by Ward, et al.[24] In this study, seizures pose a significant risk with 6.0 times higher for mortality ($p = .0001$). Other risk factors we identified were pleural effusion ($p = .0016$), myocarditis ($p = 0.0198$), hematological manifestations, in particular hemolytic anemia ($p = .0326$), and lymphopenia ($p = .0363$) are significantly factors associated to mortality

Treatment is a pivoting factor affecting survival of SLE patients. Judicious use of corticosteroids and cytotoxic agents such as cyclophosphamide and azathioprine in achieving a better control of disease activity is one of the well-recognized reasons for the improvement in survival of SLE patients in recent years.[21] However, heavy immunosuppression, such as high doses of steroids, may adversely affect short-term survival of SLE because of the risk of infection.[9] Our institution is a government-funded institution, which caters to patients of low income families, giving high-dose steroids should be given with caution. Majority of our patients succumb to septic shock secondary to nosocomial infection. We have documented cases of soft tissue infections and osteomyelitis as complications among our admitted pediatric SLE patients.

Despite the overall improvement in the survival of pediatric patients with SLE, mortality is still 10–25% within 10 years of disease onset.[10] In a study from India, the cumulative percentage survival at 1, 5 and 10 years was found to be 89, 77 and 60%, respectively.[11] Despite advances in diagnosis and management, complications still cause substantial morbidity.[20]

Survival of children with SLE has significantly improved over the years to more than 90% since the 1980s.[28] Since the mid-1990s, several centers from the industrialized world have reported 5-year survival rates in excess of 90%[16,17] compared with an appalling 40% in the 1950s.[11] A study on prognosis of pediatric SLE in the Western world reported a remarkable improvement from a 5-year survival rate of only 50% in the 1950s[22] to a 10-year survival rate of nearly 90% in the last decade.[12,16] The overall 1, 3, and 5-year survival rate of our pediatric SLE patients were 89.2%, 88.6%, and 80% respectively. These findings are relatively lower when compared to data from high income countries but comparable to the findings of the other developed countries.[8,10,22]

CONCLUSION

Mucocutaneous symptoms (88.1%) are the most common presenting features among Filipino pediatric SLE patients. Other initial manifestations are hematologic, renal, and musculoskeletal. Non-specific systemic symptoms of fever, weight loss, and generalized body malaise were also among the most common presenting symptoms. During the entire disease course, mucocutaneous (95.8%) manifestations are still the most common, followed by hematologic (80.5%), and renal (79.3%) involvements. Clinical risk factors such as seizures, myocarditis, and pleural effusion were significant causes of mortality. Hematologic laboratory findings of leukopenia and lymphopenia were also significant risk factors for mortality. The 10-year survival rate of 79% was comparable with the data from other developing countries.

Recommendations

Most published survival studies of SLE have been retrospective, and selection bias and incompleteness of medical records are major flaws. Prospective study is therefore recommended. Furthermore, continuous follow-up of our cohort of SLE patients is necessary to accrue data on long-term survival of the disease.

Limitations of the study

The retrospective nature of the study limited available crucial data. The evaluation between survival and risks factors for mortality could have been more accurate with a prospective design. Being a single center experience, it does not represent the total picture of the condition.

Statement of Authorship

Both authors contributed in the conceptualization of work, acquisition and analysis of data, drafting and revising and approved the final version submitted.

Author Disclosure

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