Ten-Year Survival Analysis of Filipino Patients with Systemic Lupus Erythematosus at the National Kidney and Transplant Institute

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Abstract

Introduction: Systemic lupus erythematosus (SLE) is increasingly being diagnosed in our country. This study aims to describe the clinical features, management strategies and outcome of patients with SLE during a ten-year period.
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Methods: This is a retrospective cohort study of patients first diagnosed with SLE at the National Kidney and Transplant Institute in 2004 who were then followed up in the next ten years.

Results: Eighty-five patients were first diagnosed with SLE in 2004. The mean age was 28.1±12.03 years old. Hypertension (34.12%) was the most common co-morbid illness. Renal involvement (74.12%) was seen in a majority but only those with cardiopulmonary manifestations (mean=0.71 years, *p*=0.030) significantly affected survival. Eleven patients (12.94%) expired during the study period. Active disease and infection were the most common causes of death. Biopsy-proven lupus nephritis had a significantly higher survival rate (mean=10.57 years, *p*=0.006). Those on hemodialysis had a significantly lower survival time (mean=8.82 years, *p*=0.040).

Discussion: The estimated 10-year cumulative survival rate of patients with SLE in our cohort was 75%. This is comparable to the rates reported in some countries. Regular follow-up at six to eight weeks intervals with more frequent follow-up for patients with an SLE flare and/or on intensive immunosuppression was the most likely reason for studies reporting higher survival rates. The disparity in the survival rates may also be attributed to the frequency of exacerbations with better survival among those who never had exacerbations. The most common cause of death was due to septic shock secondary to pneumonia. The authors believe that one factor that was contributory to death was the degree of immunosuppression as observed in studies describing high doses of corticosteroids on those who have died.

Conclusion: The cumulative survival rate decreased from 90% at the time of diagnosis to 75% on the tenth year which was comparable to several countries. Patients with cardiopulmonary manifestations were found to significantly affect survival in this study. Although renal involvement was the most common initial manifestation, it did not significantly affect survival similar to other studies. However, biopsy-proven lupus nephritis cases had better survival since this allowed treatment to be streamlined based on the class of lupus nephritis. Active disease and infection were the most common causes of death.

Keywords: systemic lupus erythematosus, sle, lupus nephritis, filipino, survival

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can affect almost any organ system. Its presentation and course are highly variable, ranging from indolent to fulminant, and a relapsing and remitting course.[1] The annual incidence averages five per 100,000 population[2] while the reported prevalence ranges from 52 per 100,000 population.[3] SLE has the potential to cause morbidity and mortality.[1,4] Management largely depends on disease severity and its clinical manifestations.[1,4]

A local study involving 1,070 Filipinos with SLE reported a mean age of 28.5 years old at the time of diagnosis, with a female to male ratio of 23:1.[5] The same cohort was studied to determine the causes of mortality and active SLE disease at the time of death and it was observed that in a majority of patients, infection was the leading contributory factor, followed by renal involvement and sepsis.[6] Another study reported a mortality rate of four percent comprised of female patients with a mean age of 46 years.[7] Septic shock secondary to severe pneumonia was the most common cause of death.[7] Overall survival rates were described in one large study after five, 10, 15 and 20 years which were 93%, 90%, 90% and 80%.[7]

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Despite the increasing number of Filipinos diagnosed with SLE in our country, there are only a few studies describing their survival. This study aims to provide a comprehensive update on the presenting clinical manifestations and estimated cumulative 10-year survival rate of Filipino patients first diagnosed with SLE at the National Kidney and Transplant Institute.

Methods

A retrospective analysis was done on all patients who were first diagnosed with SLE on admission at the National Kidney and Transplant Institute, from January 1, 2004 to December 31, 2004 after the study protocol was reviewed and approved by the Technical Review Board and Institutional Ethics Review Board. The diagnosis of SLE was based on the fulfilment of at least four out of the 11 criteria in the 1997 Update of the 1982 American College of Rheumatology Revised Criteria for Classification of Systemic Lupus Erythematosus which include: malar rash, discoid rash, photosensitivity, oral ulcers, non-erosive arthritis, pleuritis or pericarditis, renal disorder (persistent proteinuria >0.5g/day or >3+ if quantitation not performed, or cellular casts), neurologic disorder (seizures or psychosis in the absence of offending drugs or known metabolic derangements), hematologic disorder (hemolytic anemia, leukopenia (<4,000/cu. mm), lymphopenia (<1,500/cu. mm.), thrombocytopenia (<100,000/cu. mm.), immunologic disorder (anti-dsDNA, anti-Sm, anti-phospholipid antibodies) and positive antinuclear antibody. Patients who fulfilled this criteria were then retrospectively followed up for a period of 10 years. Patients who were previously diagnosed with SLE prior to 2004 and those who did not follow up in our institution were excluded.

The sample size was computed based on the total number of patients admitted who were first diagnosed of SLE from 1 January 2004 to 31 December 2004 (clinical profile) and then followed-up for 10 years. With reference to similar studies done in other countries,[12,13] a 95% survival rate with a precision of ±5% was used to confirm if the sample size in this study would be valid and the minimum sample size computed was 73.

Demographic data, reasons for admission, days of hospitalization, outcome, co-morbid illnesses, clinical manifestations and laboratory results, treatment modalities and renal replacement therapy (if applicable) were collected. Renal biopsy results whether at diagnosis or on the same year as diagnosis were also gathered if applicable. These patients were then followed in the next ten years based on chart review at the National Kidney and Transplant Institute from the time of diagnosis.

Confidentiality of patient information was upheld at all times in accordance to the Declaration of Helsinki. A code number was assigned to each patient as data were encoded in Microsoft Excel spreadsheets to maintain anonymity. Information not related to the study proper was not included.

Categorical variables will be described using frequency and percentages. Continuous variables will be described using mean and standard deviation (SD) if normally distributed, and median and interquartile range (IQR) if non-normally distributed. Life Table and Kaplan-Meier Graphs were used to calculate survival. Log-rank statistics was used to determine if a significant difference in survival exists based on clinical manifestations, lab features and treatment. Missing variables were neither replaced nor estimated. A p-value <0.05 was considered as significant. Statistical analysis was performed using SPSS v20.0.

Results

There were a total of 223 patients with a final diagnosis of Systemic Lupus Erythematosus with or without other organ or systemic involvement (ICD-10 Diagnosis Code of M32.0-M32.9) at the National Kidney and Transplant Institute from January 1, 2004 to December 31, 2004. There were 138 (61.9%) admissions and re-admissions of previously diagnosed cases of SLE which were excluded in this study. The final study sample consisted of 85 (38.1%) newly diagnosed cases from January 1, 2004 to December 31, 2004. (Table I)

The peak age of onset was between 21 to 30 years old among females and it was between 11 to 20 years old among males as shown in Figure 1. The average length of hospital stay was 7.66±13.13 days. There were six patients (7%) who expired on the same admission.

The most common reasons for admission were the presence of edema (facial edema, bipedal edema or anasarca) in 41.18%, need for kidney biopsy based on

Table I. Demographic profile of patients who were first diagnosed with SLE from 01 January 2004 to 31 December 2004 at NKTI (n=85)

Clinical characteristics	Frequency (%)
Female	77 (90.59)
Age in years (mean ± SD)	28.13 ± 12.03
Reasons for admission	
SLE-related	69 (81.18)
Non-SLE related	16 (18.82)
Co-morbid Illness	
Hypertension	29 (34.12)
Pulmonary tuberculosis	15 (17.65)
Thyroid disorders	3 (3.53)
Coronary artery disease	2 (2.35)
Type 2 diabetes mellitus	2 (2.35)
Dyslipidemia	1 (1.18)
Biopsy-proven lupus nephritis	65 (76.47)
Patients who underwent hemodialysis	12 (14.12)
Length of hospital stay in days (mean ± SD)	7.66 ± 13.13
Discharge status	
Improved	79 (93)
Expired	6 (7)

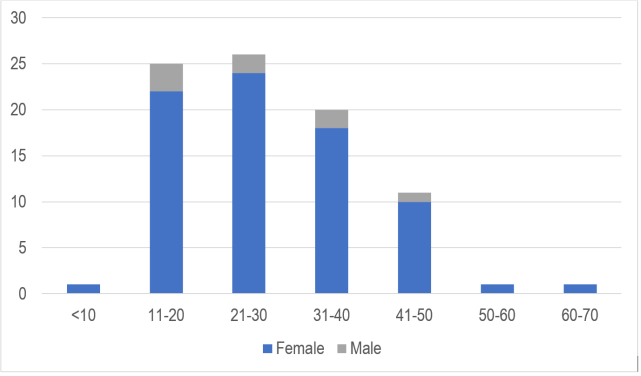

Figure 1. Age and gender distribution of patients diagnosed with SLE in 2004

significant urinalysis findings (such as persistent proteinuria and/or hematuria) in 28.24%, rashes in 8.23%, fever in 7.06%, arthralgia in 7.06%, malaise 4.71% and dyspnea in 3.53%. Hypertension (34.12%) and pulmonary tuberculosis (17.65%) were the most common co-morbid illnesses. Thyroid disorders (2.53%), coronary artery disease (2.35%), diabetes mellitus (2.35%), and dyslipidemia (1.18%) were seen in a minority.

The most common clinical manifestations at the time of diagnosis were renal (74.12%), systemic (65.88%), hematologic (62.35%) and cutaneous (28.24%) manifestations. Less frequently seen were gastrointestinal (16.47%), musculoskeletal (11.76%), neurologic (11.76%), and cardiopulmonary (8.24%) manifestations as seen in Table II.

In addition, among the 63 cases with renal manifestations, all had proteinuria and 84% had active urinary sediments. There were 12 (14.12%) patients who had end stage renal disease who subsequently underwent hemodialysis. Kidney biopsy was performed in 24 patients on admission while another 41 patients subsequently underwent kidney biopsy on the same year. Among these patients, Class IV: diffuse lupus nephritis was the most common histologic finding (35, 41%) followed by Class III: focal lupus nephritis (17, 20%). Less common were Class II: mesangial proliferative lupus nephritis (6, 7.06%), Class 5: membranous lupus nephritis (5, 5.58%), Class I: minimal mesangial lupus nephritis (1, 1.18%) and Class 6: advanced sclerotic lupus nephritis. (Table II)

Among those 56 cases with systemic features, 52% had body weakness or fatigue and 41% had fever. Moreover, all 53 cases with hematologic manifestations had anemia with a hemoglobin of <10g/dL while only 11% had leukopenia (<4000/uL). Among those cutaneous features, one half had malar rash and 29% had discoid or vasculitic rashes. (Table II)

Nausea, vomiting, bloatedness were non-specific gastrointestinal symptoms seen in all 14 cases with gastrointestinal manifestations while 64% had mild abdominal pain. Arthralgia and/or arthritis was seen in all 10 patients with musculoskeletal manifestations. Concomitant myalgia was seen in four cases (40%).(Table II)

Table II. Clinical features and immunologic tests of patients with systemic lupus erythematosus

Clinical manifestation	Frequency (%)
Renal	63 (74.12)
Proteinuria	63 (74.12)
Active urinary sediments (RBC, WBC, Casts)	53 (62.35)
Systemic	56 (65.88)
Body weakness/Fatigue	29 (34.12)
Fever	23 (27.06)
Weight loss	6 (7.06)
Anorexia	6 (7.06)
Nausea/Vomiting	4 (4.71)
Hematologic	53 (62.35)
Anemia (<13g/dL in men, <12g/dL women)	53 (62.35)
Leukopenia (<4000/ul)	6 (7.06)
Thrombocytopenia (<100,000/ul)	4 (4.71)
Lymphopenia (<1500/ul)	2 (2.35)
Cutaneous	24 (28.24)
Malar rash	12 (14.12)
Discoid/Vasculitic rash	7 (8.24)
Oral ulcers	5 (5.88)
Alopecia	2 (2.35)
Urticaria	1 (1.18)
Gastrointestinal	14 (16.47)
Non-specific (nausea, vomiting, bloatedness)	14 (16.47)
Abdominal pain (mild)	9 (10.59)
Neurologic	10 (11.76)
Headache	5 (5.88)
Seizures	2 (2.35)
Mood disorder	3 (3.53)
Cardiopulmonary	7 (8.24)
Coronary artery disease	4 (4.7)
Pulmonary hemorrhage	2 (2.35)
Pleural/Pericardial effusions	2 (2.35)
Laboratory test	
Positive ANA	85 (100)
Positive Anti-dsDNA	39 (45.88)
Elevated ESR or CRP	6 (7.06)
Low C3	4 (4.71)

As for the seven cases with cardiopulmonary manifestations, 57% have coronary artery disease while 29% have pulmonary hemorrhage, and 29% have pleural or pericardial effusions. All patients had positive anti-nuclear antibody results while 46% had positive anti-dsDNA tests. (Table II)

At the time of diagnosis, standard corticosteroid (prednisone) was given to 85% of patients. Pulse cyclophosphamide was given in 28% of patients while 22% received pulse methylprednisolone. Other medications given include mycophenolate mofetil (3.53%), hydoxychloroquine (2.35%) and azathioprine (2.35%). (Table III)

The overall mean survival time was 9.84 years with a median of 8.865 years. As time progressed, the estimated cumulative survival rate decreased from 90% at the time of diagnosis to 75% on the tenth year as shown in Figure 2.

During the ten-year follow up, there were a total of 11 patients (12.94%) who expired in our institution. All were

Table III. Treatment regimens given on initial diagnosis

Treatment	Frequency (%)
Standard corticosteroid (prednisone)	72 (84.71)
Pulse cyclophosphamide	24 (28.24)
Pulse corticosteroid (methylprednisolone)	19 (22.35%)
Mycophenolate mofetil	3 (3.53)
Hydroxychloroquine	2 (2.35)
Azathioprine	2 (2.35)

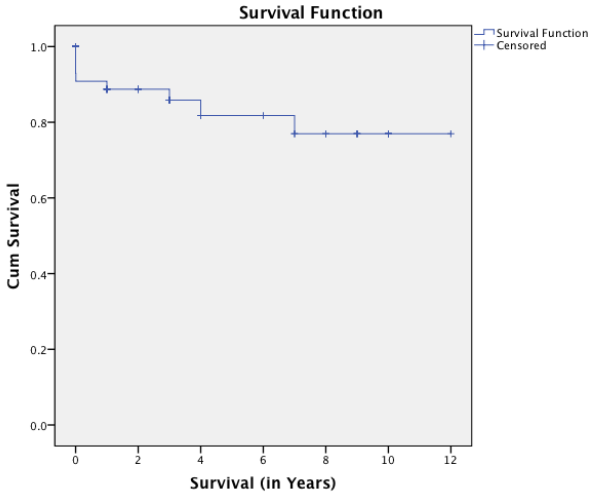

Figure 2. Cumulative survival rate in 10 years with a mean survival time of 9.842 and a median survival time of 8.625

females with a mean age was 27.64±7.62 years old. The mean length of hospital stay was 6.9±4.93 days. Among these patients, 10 had SLE with LN (Class IV) with active disease. Infection presenting as septic shock was the most common cause of death secondary to pneumonia (3), complicated urinary tract infection (1), brain abscess (1), cellulitis (1) and Goretex graft abscess (1). Gram negative organisms were isolated on these patients. Enterobacter aerogenes (1), Pseudomonas aeruginosa (1), Escherichia coli (1) and Klebsiella pneumoniae (1) were isolated. Growth of Burkholderia cepacia (1), K. pneumoniae (1) and P. aeruginosa (1) grew on endotracheal aspirate cultures. Urine culture results revealed E. coli (1) and K. pneumoniae (1). Non-infectious causes include upper gastrointestinal bleeding (2), pulmonary hemorrhage secondary to thrombotic thrombocytopenia purpura (1), and cardiac dysrhythmia on a patient with uremic cardiomyopathy (1). (Table IV)

Gender was not a significant factor that affected survival (p=0.271). When the survival periods were stratified by clinical manifestations, only cardiopulmonary involvement (mean=0.71 years, p=0.030) was found to significantly affect survival. (Table V) (Figure 3)

Higher trends of survival time were seen in those who received standard corticosteroid, pulse methylprednisolone and pulse cyclophosphamide particularly to those with renal involvement but these were not shown to be statistically significant.

Lastly, patients with biopsy-proven lupus nephritis had a significantly higher survival rate (10.57 years, p=0.006) compared to cases who were not biopsied. (Figure 4) Those with end stage renal disease undergoing hemodialysis was noted to have a significantly lower survival time (mean=8.82 years, p=0.040) compared to those who did not undergo hemodialysis. (Figure 5)

Table IV. Profile of expired patients in a 10-year period

	Frequency (%)
Total number of expired patients	11 (12.94)
Female	11 (12.94)
Mean age in years (mean ± SD)	27.64 ± 7.62
Mean length of hospitalization in days (mean ± SD)	6.9 ± 4.93
Causes of death	
Active lupus nephritis and infection	7 (8.24)
Septic shock	6 (7.06)
Pneumonia	3 (3.53)
Urinary tract infection	1 (1.18)
Cellulitis	1 (1.18)
Goretex graft abscess	1 (1.18)
Other complications	4 (4.71)
Gastrointestinal bleeding	2 (2.35)
Pulmonary hemorrhage	1 (1.18)
Cardiac dysrhythmia	1 (1.18)

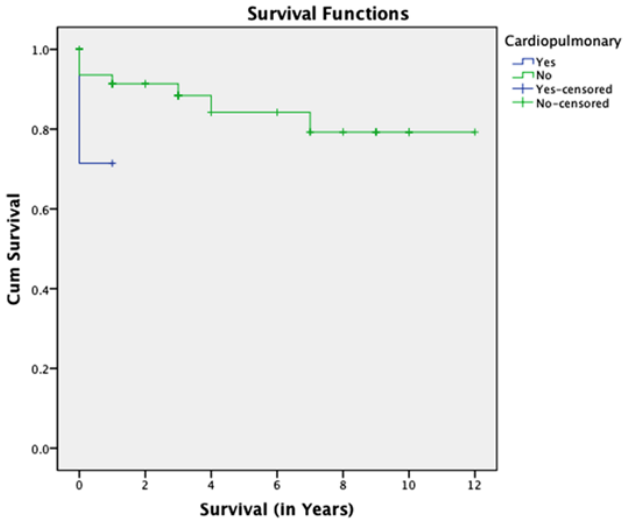

Figure 3. Survival time among patients who had cardiopulmonary manifestations (log-rank=4.522; p-value=0.033)

Table V. Mean survival time based on clinical manifestations, presence of lupus nephritis (biopsy-proven) and those who underwent renal replacement therapy

			95% Confidence Interval		Comparison of means (log ranks)	
	Estimate survival time	Std. error	Lower bound	Upper bound	Statistic	p-value
Cardio-pulmonary	0.71	0.17	0.38	1.05	4.52	0.030
Biopsy-proven lupus nephritis	(yes)		10.57	0.63	9.34	11.81
RRT (HD)	(yes)		6.81	1.94	3	10.62

Discussion

The mean age of patients diagnosed with SLE in our institution (28.13±12.03 years) was similar to a large study done (28.5±11.5 SD years) at a local university[5] and was close to the findings of a study (30±9.7 SD years) in Iran.[7] Higher mean age of 35±11 years and 33.6±1.0 year were reported in a smaller local study[8] and in a study among a southern Chinese population.[13] The female to male ratio (10:1) was close to the study done by Rillon-Tabil et al (2012) which was 14:1.[8] The same study also reported hypertension as the most common co-morbid illness secondary to lupus nephritis.[8] Other co-morbid illnesses include pulmonary tuberculosis, thyroid disorders, and coronary artery diseases.[8]

In our study, the most common reason for admission was the presence of edema which is suggestive of an underlying renal disease and was confirmed to be present during admission. The need for renal biopsy was the second most common reason of admission which was intended not only to confirm the diagnosis, but more importantly to establish the prognosis and to determine the subsequent management. In one retrospective study, SLE flare was the most common cause of admission followed by infection and renal biopsy.[10] This was congruous to a local study reporting concomitant flare and infection as the most common cause.[8]

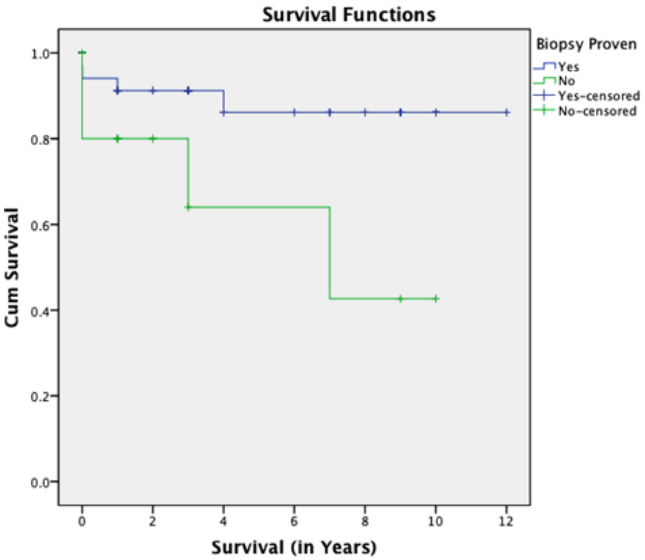

Figure 4. Comparison of survival time among patients with and without biopsy-proven lupus nephritis (Log ranks= 7.507, *P*-value=0.006)

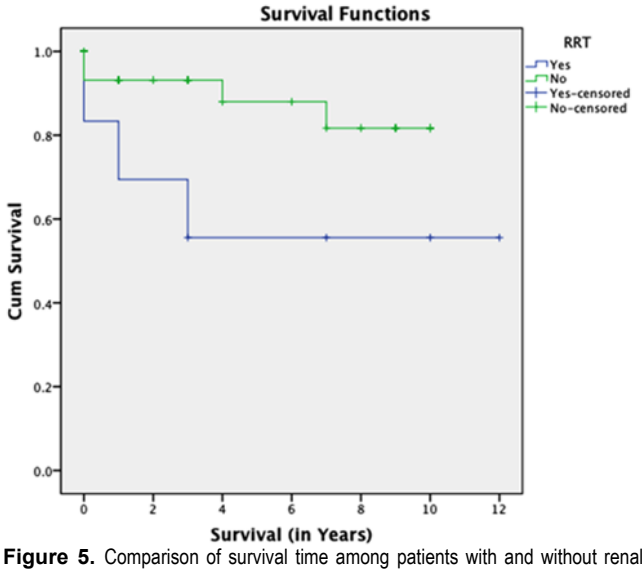

Figure 5. Comparison of survival time among patients with and without renal replacement therapy - hemodialysis (log rank=3.853; *p*-value=0.05)

In a study done among 1,070 Filipinos, arthritis (68%), malar rash (49%) and renal involvement (47%) were the most common clinical manifestations.[5] Similarly, a study in China also described parallel findings of arthritis (82%) and malar rash (55%) as the most common clinical features while renal manifestations were seen in only 27% of cases.[13] Arthritis (89.3%) was also the most common initial manifestation in a study among Indians followed by fever (50.6%), dermatologic manifestations (64%), anemia (56%) and renal involvement (33.3%).[14] While all these manifestations were seen in our study but with variable frequencies, renal manifestations (74.12%) predominated and this could be attributed to our study setting as being a tertiary center specializing in renal diseases. However, in both local[5,8] and international[13] studies describing re-admissions and flares, presence of renal involvement was seen in most patients. Class IV: Diffuse Lupus Nephritis followed by Class III: Focal Lupus Nephritis were the most common renal biopsy findings in our cohort which is consistent with the other studies done locally[15,16] and worldwide.[10]

Anemia was the most common hematologic feature seen in 53 patients in our cohort (65%) which could be multifactorial in etiology. Presence of renal disease, chronic inflammation, iron-deficiency and occult gastrointestinal bleeding are possible causes. Comparably, a local study (5) and a study in India[14] showed the same hematologic finding (29% and 56% respectively).

Some studies reported active SLE followed by infection as the most common cause of death[12, 20] while several studies reported infection to predominate over active disease as the most common cause.[10-11, 13, 17] Similarly, results indicated presence of active disease on all patients who expired. Ten of 11 cases had active lupus nephritis while only one had active SLE without renal involvement. Among the expired cases, septic shock was present in six cases (54.54%) with pneumonia (27.27%) as the most common cause of infection. We believe that one factor that was contributory to death was the degree of immunosuppression as observed in studies describing high doses of corticosteroids on those who have died.[10,13] Active SLE and acute vascular events were other commonly reported causes.[17] There were also studies describing disease-related complications such as pulmonary hemorrhage, severe pulmonary hypertension,[13] and myocardial infarction.[10] There was one case in our study who expired of pulmonary hemorrhage which was

secondary to thrombotic thrombocytopenic purpura. Two of the expired cases had upper gastrointestinal bleeding which was most likely secondary to bleeding peptic ulcer disease.

The estimated 10-year cumulative survival rate of our study is 75%. This is similar to the study of Kasitanon et al. (2003) which had a 10-year survival rate of 74.9%.[18] This is comparable to two earlier studies done by Ward et al.(1995) and Jacobsen et al.(1998) which revealed a 10-year survival rate of 71% and 76%.[19, 20] In contrast, higher 10-year survival rates of 89% at 10 years were described in China.[21] A prospective study done in the same country for seven years supported the same findings with high trends in survival, notably 97% at three years, and 93% at five and seven years.[13] These patients were followed-up prospectively at regular intervals of six to eight weeks with more frequent follow-up arranged for those who had a flare or were receiving intensive immunosuppression.[13] Mortality studies done by Abu-Shakra et al. (1995) in a single center revealed a 10-year survival rate of 85%.[17] The disparity in the survival rates may be attributed to the frequency of exacerbations as discussed in the study of Swaak et al. (1989) which revealed higher 10-year survival rates among patients who never had exacerbations (100% at 10 years) than those with one, two or three exacerbations with rates of 91%, 69% and 33% respectively during his 10-year follow-up.[22] In a local five-year study done by Adiong et al. (2009), the estimated cumulative survival rate was 78% among cases of lupus nephritis.[15] It is noteworthy that in our study, our four to six-year cumulative rate of SLE in general was 80%, a finding very close to the earlier report.

Jacobsen et al. (1998) also found renal manifestations, particularly the presence of proteinuria and nephritis, to be unrelated to survival,[20] although renal involvement was predominantly seen in those who died as also observed by Swaaket et al.[22] While it was observed that nephritis contributes to organ damage, it is not a major determinant factor for survival.[13] These studies were consistent with the present study.[13, 20, 22]

Since most of the patients in our study had lupus nephritis, we compared treatment regimens to a local study describing the spectrum of renal involvement among Filipino patients with SLE and found similar findings in accordance to the lupus nephritis management guidelines published by the Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA-EDTA)[23] such as use of oral corticosteroids (prednisone), pulse methylprednisolone and pulse cyclophosphamide. To the best of our knowledge, there have been no local studies describing the mean survival time of SLE patients based on treatment modalities given. Furthermore, treatment regimen used was not found to affect survival time significantly.

In contrast to an earlier report,[19] gender was not a significant factor affecting survival of SLE patients in our study. A prospective study among patients with SLE in a southern Chinese population also reported no gender difference in major organ manifestations, damage scores and survival rates.[13, 24]

Four of the twelve patients who underwent hemodialysis expired due to active disease with concomitant infection with Goretex graft abscess (1) and pneumonia (1), pulmonary hemorrhage (1) and gastrointestinal bleeding (1). This is consonant to the study of Chang which reported that the major threat to SLE patients on maintenance dialysis was infections.[25]

Conclusion

The estimated 10-year cumulative survival rate of SLE patients in our cohort was comparable to reports done in several countries. Active disease and infection were the most common causes of death. Only those with cardiopulmonary manifestations were found to significantly affect survival in this study. Notably, renal involvement was not found to significantly affect survival in our cohort which is congruous to other studies. Treatment regimen at the time of diagnosis also did not have any significant effect. Biopsy-proven lupus nephritis cases had better survival in this study mainly because this allowed treatment to be streamlined based on the class of lupus nephritis. The lower survival rate noted in our study was most likely secondary to poor follow-up and poor compliance to either maintenance medications or hemodialysis among patients with end stage renal disease.

Recommendations

The author recommends a multi-center study to discount the possibility of bias that our study was conducted in a tertiary referral center for renal diseases which can explain why renal involvement was the most common presenting clinical feature.

Furthermore, a study documenting the number of flares and treatment modalities given during the follow-up period is also recommended as this may be inversely proportional to survival. Documentation of the degree of immunosuppression during flares and during subsequent follow-up are also recommended especially if these are given in high doses, predisposing one to have overwhelming infections. Treatment-related complications are also important in long-term studies since this can potentially affect survival.

Factors such as socioeconomic status, educational background and psychosocial support were not taken into account in this study which we believe may potentially affect survival. Taking these into consideration in future studies may help the patient better understand the disease, hence, enhance compliance especially to maintenance

immunosuppressants and hemodialysis, if applicable.

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