PREDICTIVE FACTORS AND RENAL OUTCOMES IN CHILDHOOD SYSTEMIC LUPUS ERYTHEMATOSUS

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DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE DEGREE OF MASTER'S IN MEDICINE (PAEDIATRICS)



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LIST OF ABBREBIATION AND NOMENCLATURE

ACR	: American College of Rheumatology
AIHA	: Autoimmune Hemolytic Anemia
ANA	: Anti-Nuclear Antibody
Anti-Sm	: Anti- Smooth Muscle
ARF	: Acute Renal Failure
B40	: Bottom 40
BP	: Blood Pressure
C3, C4	: Complement 3, Complement 4
CI	: Confidence Interval
CIC	: Circulating Immune Complexes
CKD	: Chronic Kidney Disease
CNS	: Central Nervous System
cSLE	: Childhood Systemic Lupus Erythematosus
DIL	: Drug-Induced Lupus
dsDNA	: Double Stranded DNA
eGFR	: Estimated Glomerular Filtration Rate
ERA-EDTA	: European Renal Association- European Dialysis and Transplant
	Association
ESRD	: End Stage Renal Disease
EULAR	: European League Against Rheumatism
FBC	: Full Blood Count

FcγR	: Fc Gamma Receptor
FcγRIIIa	: Fc Gamma Receptor IIIa (CD16)
Freq.	: Frequency
GFR	: Glomerular Filtration Rate
HD	: Hemodialysis
HPE	: Histopathological Examination
HRPZ II	: Hospital Raja Perempuan Zainab II
HUSM	: Hospital Universiti Sains Malaysia
IgG	: Immunoglobulin G
IQR	: Interquartile Range
KDIGO	: Kidney Disease Improving Global Outcomes
JIA	: Juvenile Idiopathic Arthritis
LN	: Lupus Nephritis
MCTD	: Mixed Connective Tissue Disease
M40	: Middle 40
OR	: Odd Ratio
RBCs	: Red Blood Cells
RF	: Rheumatoid Factor
SD	: Standard Deviation
SLE	: Systemic Lupus Erythematosus
SLICC	: Systemic Lupus International Collaborating Clinics
T20	: Top 20
Urine PCI	: Urine Protein Creatinine Index

ABSTRAK

Faktor – faktor risiko berkaitan masalah Lupus Nephritis dan kesan kepada buah pinggang di kalangan *Systemic Lupus Erythematosus* Kanak-kanak.

Objektif: Kajian ini bertujuan untuk menilai faktor penentu dan kesan kepada buah pinggang di kalangan pesakit *Systemic Lupus Erythematosus* (SLE) kanak-kanak. Kajian ini bertujuan untuk mengenal pasti ciri-ciri klinikal awal, nilai ujian makmal, dan mekanisme molekul yang dikaitkan dengan prognosis buah pinggang teruk, dalam usaha mengoptimumkan pengawasan dan pemantauan dalam pesakit *Systemic Lupus Erythematous* kanak-kanak ini.

Kaedah: Kajian secara retrospektif telah dijalankan di Hospital Universiti Sains Malaysia (USM), Kelantan, Malaysia. Seramai 101 pesakit telah disahkan menghidap *Systemic Lupus Erythematosus* berumur di bawah 18 tahun telah diambil untuk kajian ini. Data demografik (umur, jantina, bangsa, ketinggian, berat badan, indeks jisim badan, pendapatan bulanan ibu bapa, sejarah keluarga *Systemic Lupus Erythematosus*, dan tekanan darah), umur semasa diagnosis *Lupus Nephritis*, tempoh antara permulaan *Systemic Lupus Erythematosus* (SLE) dan *Lupus Nephritis*, faktor klinikal (hipertensi, anemia), faktor nilai ujian makmal (protinuria, hipoalbuminemia, hematuria eGFR, tahap serum kreatinin, positif dsDNA, dan biopsi buah pinggang mengikut Kelas Histologi WHO) telah diperoleh dan direkod daripada rekod perubatan pesakit.

Diskriptif dan analisis regresi logistik mudah digunakan untuk menyiasat faktor-faktor yang mempengaruhi penglibatan masalah buah pinggang di kalangan pesakit *Systemic Lupus Erythematosus*. Analisis regresi logistik berganda telah digunakan untuk memeriksa hubungan antara pelbagai faktor risiko dalam menentukan faktor penentu kepada masalah buah pinggang.

Keputusan: Seramai 101 kanak-kanak dan remaja yang menghidap *Systemic Lupus Erythematosus* telah dikenal pasti. Majoriti merupakan perempuan 93.1% dengan purata umur 12.4 tahun. 65 daripadanya mempunyai *Lupus Nephritis* yang dipastikan dengan keputusan biopsi buah pinggang Kelas IV dan ke atas iaitu 53 (81.5%) daripadanya. Faktor tekanan darah tinggi, bacaan eGFR yang tidak normal, dan penemuan histologi pada awalnya telah dikenal pasti sebagai faktor penting, dua daripadanya meprupakan faktor penentu kepada komplikasi penyakit buah pinggang kronik. Analisis Kaplan-Meier menunjukkan kadar kematian pada masa 5 tahun dan 10 tahun adalah 64% dan 43%.

Kesimpulan: *Lupus Nephritis* mempunyai kesan klinikal yang teruk dan kadar kematian yang tinggi. Penemuan histologi buah pinggang dan fungsi buah pinggang tahap empat dan ke atas telah menunjukkan hubungan yang jelas terhadap penurunan fungsi buah pinggang dan penyakit buah pinggang yang kronik. *Lupus Nephritis* di kalangan kanak-kanak yang mempunyai penyakit buah pinggang kronik, menunjukkan risiko kadar kematian hampir 50% dalam masa 5 tahun.

Kata kunci: Systemic Lupus Erythematosus Kanak-kanak, Lupus Nephritis, Faktorfaktor risiko.

ABSTRACT

Predictive Factors of Lupus Nephritis and Renal Outcomes in Childhood Systemic Lupus Erythematosus (cSLE).

Objective: This study aims to define predictive factors of kidney involvement in a cohort of paediatric patients with SLE. Studies have sought to identify early clinical features, laboratory tests, and molecular mechanisms that are associated with unfavorable renal prognosis, to optimize the surveillance and interventions in these patients.

Method: A retrospective cross-sectional study was conducted at Hospital Universiti Sains Malaysia (USM), Kelantan, Malaysia. A total of 101 patients were diagnosed with Systemic Lupus Erythematosus. aged below 18 years old were recruited for this study. Demographic data (age, gender, race, height, weight, body mass index, parent's monthly income, family history of Systemic Lupus Erythematosus and blood pressure), age during diagnosis of Lupus Nephritis, duration between onset of SLE and Lupus Nephritis, clinical factors (hypertension, anemia), Laboratory factors (proteinuria, hypoalbuminemia, hematuria eGFR, serum creatinine level, dsDNA positivity, and Histological WHO Class renal biopsy) were obtained from the patient's medical records. Descriptive and simple linear regression was used to investigate predictors for renal outcomes, and prognostic analyses were performed. Multivariate logistic regression analysis was performed to determine independent predictors of renal outcomes.

Result: One hundred and one children and adolescents with SLE were recruited in the cohort. Majority of them were females (93.1% with mean age 12.4 years old). 65 of them have lupus nephritis with biopsy proven of class IV and above in 53 (81.5%) of them. Presence of hypertension, abnormal eGFR, and histological biopsy of diffuse proliferative glomerulonephritis were initially identified as significant variables, however, only the latter two factors were found to be significantly predicting complication of CKD (OR 11.8, 95 %CI 2.22-63.5), (OR 29.9, 95% CI 3.05-294), respectively. The Kaplan Meier mortality survival analysis among patients with CKD also demonstrated 5- and 10-years mortality were 64% and 43%, respectively.

Conclusion: Lupus Nephritis has been demonstrated to be associated with poor clinical outcomes and high mortality. Histological findings of diffuse proliferative disease and abnormal eGFR of stage IV onwards had been shown to be significantly associated with CKD. Lupus Nephritis children with CKD had mortality rate of almost 50% within 5 years.

Keywords: Childhood Systemic Lupus Erythematosus (cSLE), Lupus Nephritis, chronic kidney disease, risk factors.

CHAPTER II

THE TEXT

2.1

Section A Introduction

Introduction:

Systemic Lupus Erythematosus (SLE) is a chronic inflammatory disease caused by decreased immune tolerance, production of antibodies, deposition of immune complexes on target tissues, and activation of the complement system. Various organs known to be affected include skin, joints, heart, lungs, kidneys, and nervous system. Involvement of the kidneys called lupus nephritis (LN) is one of the most severe clinical manifestations with higher morbidities and mortality in paediatric age populations (1).

About 10–15% of all SLE patients are diagnosed in childhood (2). Onset in childhood compared to adults is associated with more frequent and severe renal and central nervous system involvement (3). Indeed, studies have found a worse outcome of childhood SLE (cSLE) as compared to lupus in adults (4). Childhood systemic lupus erythematosus (cSLE) is the most common autoimmune disease leading to chronic kidney disease in children. The risk of progression to chronic kidney disease (CKD) in patients with LN is 18–50% (5–7).

Early diagnosis and prompt treatment of the disease is crucial because survival has been shown to be significantly reduced in paediatric patients with SLE and kidney disease compared to those without kidney disease.

End stage renal disease (ESRD) occurs in 10%–20% of patients with severe renal disease after a mean period of 5 years (5,8). Hence, clarification of renal prognosis is of considerable relevance. Various factors have been reported to be associated with ESRD in patients with LN: hypertension, decreased C3 complement level, nephrotic syndrome,

anemia, and diffuse proliferative nephritis (5,9). In most previous reports, impaired renal function at initial evaluation was a significant prognostic parameter for renal failure.

In other study, several other factors that contributed to worsen the outcomes of lupus nephritis include serum creatinine 1.5 mg/dl, serum urea 100 mg/dl, Class IV or more in renal biopsy, severe hypertension, recurrent attack lupus nephritis and demographical feature like age, sex and racial were reported in many studies(10).

The main purpose of this study is to evaluate renal outcomes, and studies predictive factors in lupus nephritis to improve the outcomes of disease in our population.

Section B Study Protocol

2.2.1

Documents submitted for Ethical Approval

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UNIVERSITI SAINS MALAYSIA

2020

Research Title

Predictive Factors of Lupus Nephritis and Renal Outcomes in Childhood Systemic

Erythematosus (cSLE).

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Introduction:

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About 10–15% of all SLE patients are diagnosed in childhood (2). Onset in childhood compared to adults is associated with more frequent and severe renal and central nervous system involvement (3). Indeed, studies have found a worse outcome of childhood SLE (cSLE) as compared to lupus in adults (4). cSLE is the most common autoimmune disease leading to chronic kidney disease in children. The risk of progression to chronic kidney disease (CKD) in patients with LN is 18–50% (5-7).

Early diagnosis and prompt treatment of the disease is crucial because survival has been shown to be significantly reduced in paediatric patients with SLE and kidney disease compared to those without kidney disease.

End stage renal disease (ESRD) occurs in 10%–20% of patients with severe renal disease after a mean period of 5 years (5,8,9). Hence, clarification of renal prognosis is of considerable relevance. Various factors have been reported to be associated with ESRD in patients with LN: hypertension, decreased C3 complement level, nephrotic syndrome,

anemia, and diffuse proliferative nephritis (5,8,10,12). In most previous reports, impaired renal function at initial evaluation was a significant prognostic parameter for renal failure.

In other study, several other factors that contributed to worsen the outcomes of lupus nephritis include serum creatinine 1.5 mg/dl, serum urea 100 mg/dl, Class IV or more in renal biopsy, severe hypertension, recurrent attack lupus nephritis and demographical feature like age, sex and racial were reported in many studies (12,13,14).

The main purpose of this study is to evaluate renal outcomes, and studies predictive factors in lupus nephritis to improve the outcomes of disease in my country.

Dissertation Research Proposal

TITLE: Predictive Factors and Renal Outcomes in Childhood Systemic Lupus Erythematosus (cSLE)

INTRODUCTION

1.1 Background

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease that affects multiple organs including the skin, joints, lungs, heart, kidneys, and central nervous system (1). About 10–15% of all SLE patients are diagnosed in childhood (2). Onset in childhood compared to adults is associated with more frequent and severe renal and central nervous system involvement (3). Indeed, studies have found a worse outcome of childhood SLE (cSLE) as compared to lupus in adults (4). Childhood systemic lupus erythematosus (cSLE) is the most common autoimmune disease leading to chronic kidney disease in children. The risk of progression to chronic kidney disease (CKD) in patients with LN is 18–50% (5-7).

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Paediatric Lupus in Asia⁽¹²⁾

The prevalence of childhood SLE (cSLE) was 6.3–19.3 per 100,000 in Asia. The ratio of female to male was 4.7–6.2. The mean age at diagnosis of childhood-onset SLE was 8.6–13.5 years. The most common clinical features of pediatric-onset SLE in Asia were cutaneous rashes, arthritis, hematological involvement, and nephritis.

The occurrence of nephritis varies from 29% to 81%. The most common histopathology of lupus nephritis was diffuse proliferative glomerulonephritis (WHO Class-IV) which occurred in 39.4–54% of cases of lupus nephritis.

Paediatric Lupus in Malaysia (Kelantan) (13)

The median age of the children was 12 years. Male: female ratio was 1:10. Among the clinical manifestations at presentation, hematological and renal findings (60% each) were the most common. 24% of patients developed acute kidney injury (AKI) and required either hemodialysis or peritoneal dialysis for symptomatic uremia and fluid overload.

Predictor factors

Although several studies have reported factors affecting outcomes, the results remain unclear. Contributing factors to variable outcomes or worsening lupus nephritis include serum creatinine 1.5 mg/dl (88umol/L), serum urea 100mg/dl (16mmol/L),

class IV or more in renal biopsy, severe hypertension, recurrent attack lupus nephritis (renal relapse), demographical features like age, sex and racial were reported in many studies.

Treatment

The treatment protocol issued by the European league against rheumatism and European renal association-European dialysis and transplant association (eular/era-EDTA). Recommendations for management of Lupus Nephritis (LN) consisted of:

- i- pulse glucocorticoids followed by oral Prednisolone (1 mg/kg/d) in addition to an immunosuppressive medication,
- ii- pulses of monthly cyclophosphamide (0.75/m2-1 gm/m2 of body surface) or mycophenolate mofetil (1.5-3 gm/day) or azathioprine (2-3 mg/kg/d) as induction therapy.

1.2 JUSTIFICATION TO CONDUCT THE STUDY:

Between 50–80% of children and adolescents with SLE will have kidney involvement at some point during their lifetime. Recognition and treatment of kidney disease is important because survival has been shown to be decreased in pediatric patients with SLE and kidney disease compared to those without kidney disease.

Ethnicity, histopathologic classification, male sex, hypertension, reduced renal function at baseline, treatment response, and relapse have all been considered as factors affecting severity and outcome of Lupus Nephritis. Understanding of these predictive factors may help to improve the outcome of the disease.

In order to improve renal outcomes among Pediatric lupus nephritis in cSLE, a better understanding of clinical and laboratory factors are required. Description of the predictive factors of Lupus Nephritis in childhood SLE (cSLE) are utterly essential, so that prompt treatment can be offered to improve the outcome of these children and increase the survival rate. This study entails cohort of pediatric population in Kelantan, aimed to provide data on clinical and laboratory factors, to predict progression of lupus nephritis in cSLE among children in Malaysia.

1.2.1 Locality.

Most of the study had been done in United State of America, Europe, and as well Middle east countries. There is constricted and limited data being collected among Malaysian population. Since the risk factor of cSLE itself is associated with races and gender. Data from this study will be reflected the occurrence of the disease in our community, which later can be used as an appropriate data reference for Malaysians. This study will benefit in developing a systematic guideline in Malaysia.

Referring to one study by Ikram et al in 2017, the study has different objectives whereby this study will be focusing on predictor factors of lupus nephritis and estimating survival time to mortality in CKD among LN patients.

1.2.2 Patient related.

This study may help to allocate the risky patient (patient with significant of risk factor whose has good renal outcome and as well as poor renal outcome) and further will guide us to different management later.

1.2.3 Disease related.

As the disease burden has been rising significantly by years, this study will help the health provider or policy maker in planning and structuring the financial economic support.

1.2.4 Long term complications or outcomes.

Frequent relapse or non-remission lupus nephritis, has a higher risk of developing end stage renal disease (ESRD). By that, this study will help to identify the risk factors associated with poor renal outcome and allocate to the risk group of lupus nephritis. This later would prevent end stage renal disease (ESRD).

1.3 RESEARCH QUESTION(S)

1.3.1 What is prevalence of lupus nephritis among children with Childhood SLE in Kelantan (Malaysia)?

1.3.2 What are the predictor factors associated with Lupus Nephritis in Childhood Systemic Lupus Erythematosus (cSLE)?

1.3.3 What are correlations between risk factors and renal outcomes among pediatric patients with Lupus Nephritis?

1.4 RESEARCH HYPOTHESIS

There are significant factors (age of diagnosis, gender, nutritional status, socioeconomic, hypertension, anemia, proteinuria, hypoalbuminemia, hematuria, low eGFR, low serum creatinine and positive anti dsDNA) associated with Lupus Nephritis in Childhood SLE.

There are significant prognostic factors (age of diagnosis, gender, nutritional status, socioeconomic, hypertension, anemia, proteinuria, hypoalbuminemia, hematuria, low eGFR, low serum creatinine, positive anti dsDNA, and histological class of renal biopsy) of renal outcome (relapse and remission) in Pediatric patient with Lupus Nephritis.

1.5 STUDY OBJECTIVES (GENERAL):

To describe demographic influence, predictor factors and renal outcome of Lupus Nephritis in Pediatric SLE in Hospital USM, Kelantan.

1.6 STUDY OBJECTIVES (SPECIFIC):

1.6.1 To determine the prevalence of lupus nephritis among children diagnosed with childhood SLE (cSLE) in Hospital USM, Kelantan.

1.6.2 To determine predictor factors associated with Lupus Nephritis in childhood Systemic Lupus Erythematosus (cSLE).

1.6.3 To determine time/duration to mortality in paediatric patients with CKD among Lupus Nephritis patients.

1.7 LITERATURE REVIEW

Торіс	Research Result	Journal/Article
Predictors of	A retrospective cohort study to identify	Predictors of
kidney disease in	potential clinical and laboratory predictors	kidney disease in
a cohort of	of renal disease in a cohort of pediatric	a cohort of
Pediatric patient	patients followed over 10 years.	pediatric patients
with lupus.	-47 pediatric patients with SLE were	with lupus.
	recruited into this cohort study from Johns	(SD Sule et al.
	Hopkins Children's Center and Children's	2015. SAGE
	Hospital of Philadelphia	publication 1-
	-between January 2002 till December	7 2015)
	2012.	7,2015)
	-91% female and 100% of male in the	
	cohort developed renal disease, and all	
	within one month of the diagnosis of SLE.	
	-In logistic regression, low serum	
	albumin, positive dsDNA antibodies were	
	associated with kidney disease.	

Topic	Research Result	Journal/Article
Predictive Factors	A retrospective study to evaluate lupus	(Zaim et al.
and Long-Term	nephritis and to study outcome and predictive	Rheumatology
Outcome in	factors of lupus nephritis.	(Sunnyvale)
Lupus Nephritis	-Conducted at The 7 th October University	Journal 2161-
In Libya.	Hospital and Nephrology clinic at nephrology	1149, 2018)
	center, between June 2013 and December 2016.	
	-76 patients with diagnosed lupus nephritis were	
	included in the study.	
	- Outcome lupus nephritis was complete	
	response (64.5%)	
	- Partial response was (13.2%),	
	- Resistance lupus nephritis was (22.1%),	
	- End stage renal failure on hemodialysis was	
	(7.9%),	
	- Conservative chronic renal failure was	
	(14.5%)	
	- Mortality of lupus nephritis was (13.2%)	

Topic	Research Result	Journal/Article
3. Outcome of	A retrospective study to determine the	(Ataei et al.
lupus nephritis in	clinical and histopathological features and	Pediatr
Iranian children:	outcome of children with lupus nephritis	Nephrol
prognostic	(LN).	(2008)
significance of	- 58 children under 15 years of age with	23:749–755.)
certain features.	biopsy-proven LN who had been followed up	
	at Children's Hospital Medical Center,	
	Tehran, Iran between October 1989 and	
	January 2005.	
	- Presence of hypertension at the time of	
	biopsy (P=0.04) was the only parameter	
	significantly associated with a worse renal	
	outcome.	
	- While the other parameters; anemia,	
	eGFR, proteinuria, histopathology findings,	
	Chronicity index and activity index were	
	not significantly associate with poor renal	
	outcome.	

Торіс	Research Result	Journal/Article
4. Risk Factors for	A cross-sectional observational	(Vozmediano et
Renal Failure in	study based on data from the Spanish	al. Nephron
Patients with Lupus	Registry of Glomerulonephritis for	Extra Journal,
Nephritis: Data	the years 1994–2009.	2012;2:269–
from the Spanish	-study was to analyze the	277)
Registry of	demographic characteristics,	
Glomerulonephritis.	clinicopathological correlations, and	
	risk factors associated	
	with renal failure in patients with LN	
	at the time of renal biopsy.	
	-1,648 biopsies showed LN lesions.	
	In total, 609 patients (37%) showed	
	renal failure at the time of renal	
	biopsy.	
	-Patients were aged 34 ± 13	
	years at the time of renal biopsy.	
	- Age of presentation, proteinuria	
	and hypertension were found to be	
	associated with renal dysfunction	
	(eGFR < 60 ml/min/1.73 m2).	

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Topic	Research Result	Journal/Article
5. Three Decades	A retrospective analysis to compare renal and	(Tanya
of Progress In	patient survival in a cohort of pediatric patients	Pereira et al.
Treating	followed over 3 decades.	2011. cJASN
Childhood- Onset	-138 patients diagnosed with systemic lupus	6:2192-
Lupus Nephritis	erythematous (SLE) who received care at	2199,2011)
	Holtz Children's Hospital at University of	
	Miami Miller School of Medicine between	
	January 1980 to December 2010.	
	-Ethnicity, eGFR <60ml/min per1.73m2, and	
	proteinuria were significantly associated with	
	progression to ESRD.	
	-While renal biopsy classification was not	
	significantly associated with progression of	
	ESRD (p =0.35).	

Торіс	Research Result	Journal/Article
6. Predictors of	A retrospective study, to compare outcomes in	(Kiesha et al.
Relapse and End	patients with partial versus complete treatment	Clin J Am
Stage Kidney	response.	Soc Nephrol
Disease in	- To evaluate patterns and predictors of relapse.	4: 1962–
Proliferative	-109 consented and eligible patients were	1967, 2009)
Lupus Nephritis:	identified through the Glomerular Disease	
Focus on	Collaborative Network (GDCN) and the	
Children,	University of North Carolina	
Adolescents, and	at Chapel Hill (UNC) neuropathology database	
Young Adults	between 1985- 2007.	
	- A total of 73 study participants aged 6 to 21	
	years were evaluated in this analysis.	
	- Treatment resistance and renal relapse were	
	highly predictive of ESRD.	
	- While the other factors were not significant.	

OBJECTIVE OF STUDY: 2.1 CONCEPTUAL FRAMEWORK



3. METHODOLOGY

3.1 STUDY DESIGN:

The study design used is retrospective cohort design.

3.2 PERIOD:

Study will be conducted from October 2020 until June 2021 (9 months)

3.3 LOCATION:

Hospital USM, Kubang Kerian, Kelantan

3.4 STUDY POPULATION:

The reference population are all children with childhood SLE (cSLE) age up to 18 years old, who are under follow up from 1996 until 2020 that fulfills the inclusion and exclusion criteria.

3.5 INCLUSION/ EXCLUSION CRITERIA

- 3.5.1 Inclusion criteria:
 - i- Children aged up to 18 years old.
 - ii- Diagnosis Systemic Lupus Erythematosus before 18 years old based on SLICC criteria.
 - iii- Renal biopsy histopathology based on WHO classification.

3.5.2 Exclusion criteria

- i- Patient with incomplete data.
- ii- Drugs induced Systemic Lupus Erythematosus, Discoid

Lupus or mixed connective tissue disease.

3.6 SAMPLING FRAME:

All children with childhood SLE aged up to 18 years old, who are under follow up from 1996 until 2020 that full fills the inclusion and exclusion criteria.