CHILDHOOD SYSTEMIC LUPUS ERYTHEMATOSUS (cSLE) AND ITS PSYCHOLOGICAL IMPACT: DUAL TERTIARY CENTRE EXPERIENCE

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DISSERTATION SUBMITTED IN PARTIAL

FULFILLMENT OF THE REQUIREMENT FOR THE DEGREE OF

MASTER IN MEDICINE (PAEDIATRICS)

UNIVERSITI SAINS MALAYSIA

2023

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ACKNOWLEDGMENT

In the name of Allah, the most gracious and most merciful. I would like to take this opportunity to express my thanks and gratitude to the Almighty for giving me the wisdom and confidence to complete this study. I would like to extend my to token of appreciation to following individuals :

My respected supervisor Dr Mohamad Ikram bin Ilias, Consultant Paediatric Nephrologist and Lecturer in the Department of Paediatric, School of Medical Sciences, Universiti Sains Malaysia, for his advice, guidance and support throughout this study.

My co-supervisor Associate Professor Dr Azizah Binti Othman, Clinical Psychologist and Senior Lecturer in the Department of Paediatric, Associate Professor Dr Azriani Binti Ab Rahman, Department of Community Medicine, School of Medical Sciences, Universiti Sains Malaysia for her guidance in data interpretation and analysis.

I also would like to extend my special thanks to my fellow lecturers, colleagues, staff members of Hospital Universiti Sains Malaysia (USM) and Hospital Raja Perempuan Zainab II (HRPZII), family, and friends for their encouragement and supports along the way.

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LIST OF ABBREVIATIONS AND NOMENCLATURE

USM : Universiti Sains Malaysia

SLE : Systemic Lupus Erythematosus

CDI : Children Depression Inventory

MASC : Multidimensional Anxiety Scale for Children

ASEBA : Achenbach System of Empirically Based Assessment

CBCL : Childhood Behaviour Checklist

QOL : Quality of life

HRQOL : Health-related Quality of life

CHAR : Childhood Health Assessment Questionnaire

SLEDAI : Systemic Lupus Erythematosus Disease Activity Index

ANA : Anti-nuclear antibody

Anti ds-DNA : Anti-double stranded antibody

ACR : American College of Rheumatology

WHO : World Health Organization

CI : Confidence Interval

SLICC : Systemic Lupus International Collaborating Clinics

ABSTRAK

Pengenalan: Kajian ini menyiasat potensi masalah psikologi pada kanak-kanak dengan lupus eritematosus sistemik (SLE) berbanding kanak-kanak yang sihat.

Kaedah: Kajian sampel bukan kebarangkalian telah dilakukan ke atas kanak-kanak dengan SLE, dan rakan sebaya mereka berumur 6 hingga 18 tahun. Senarai Semak Tingkah Laku Kanak-kanak untuk Umur 6–18 (CBCL 6–18) telah dilengkapkan oleh ibu bapa peserta. Soal selidik membantu menilai isu emosi dan psikologi kanak-kanak. Di samping itu, maklumat demografi dan klinikal mereka juga dikumpulkan. Analisis skor CBCL dilakukan menggunakan ujian-t bebas.

Keputusan: Seramai 111 kanak-kanak telah diambil, 41 daripadanya menghidap SLE. Kebanyakan peserta SLE adalah perempuan Melayu berumur 13–15 tahun yang bersekolah menengah. Kebanyakan mereka daripada status sosioekonomi rendah. Penemuan mendedahkan bahawa kanak-kanak dengan SLE mendapat markah yang jauh lebih tinggi daripada kanak-kanak yang sihat (kumpulan kawalan) pada tiga subskala CBCL. Subskala yang dinyatakan ialah subskala dalaman [perbezaan min 3.13, 95% selang keyakinan (CI) [0.30, 5.95] dan P = 0.03], subskala ditarik balik [perbezaan min 1.50, 95% CI [0.42, 2.60] dan P = 0.01], dan masalah perhatian [perbezaan min 2.14, 95% CI [0.35, 3.94] dan P = 0.02]. Selain itu, markah peserta SLE pada subskala lain, termasuk kebimbangan dan somatik, juga jauh lebih tinggi daripada kumpulan kawalan, walaupun perbezaan ini tidak signifikan secara statistik.

Kesimpulan: Kanak-kanak SLE dilihat mempunyai masalah psikologi yang lebih besar berbanding rakan sebaya mereka yang sihat. Mereka lebih menarik diri secara sosial dan lalai, seperti yang ditunjukkan oleh skor CBCL.

Kata kunci : Sistemik Lupus Erythematosus, masalah psikologi, domain dalaman, domain luaran, penilaian CBCL.

ABSTRACT

Introduction: This study investigated the potential psychological problems in children with systemic lupus erythematosus (SLE) compared to healthy children.

Methods: A non-probability sample study was performed on children with SLE, and their peers aged 6 to 18 years. The Child Behaviour Checklist for Ages 6–18 (CBCL 6–18) was completed by the participant's parents. The questionnaire helps to assess the children's emotional and psychological issues. In addition, their demographic and clinical information was also gathered. The analysis of CBCL scores was performed using independent t-tests.

Results: A total of 111 children were recruited, 41 of whom had SLE. Most of the SLE participants were Malay females aged 13–15 who are attending secondary school. Most of them are from low socioeconomic status. The findings revealed that the children with SLE scored substantially higher than the healthy children (the control group) on three CBCL subscales. The subscales mentioned are internalising subscale [mean difference of 3.13, 95% confidence interval (CI) [0.30, 5.95] and P = 0.03], withdrawn subscale [mean difference of 1.50, 95% CI [0.42, 2.60] and P = 0.01], and attention problem [mean difference of 2.14, 95% CI [0.35, 3.94] and P = 0.02]. Besides that, SLE participants' scores on other subscales, including anxiety and somatic, were also considerably higher than the control group, although these differences were not statistically significant.

Conclusion: Children with SLE are perceived to have greater psychological problems compared to their healthy peers. They were more socially withdrawn and inattentive, as indicated by the CBCL scores.

Keywords: Systemic Lupus Erythematosus, psychological problems, internalising domains, externalising domains, CBCL assessment.

CHAPTER II

THE TEXT

2.1

Section A
Introduction

INTRODUCTION:

Systemic lupus erythematosus (SLE) is a chronic (long-term) autoimmune ailment that affects more than one organ. In this disease, the immune system, which serves as the body's defense against infection and disease, attacks its tissues. It will have an impact on anyone, no matter their age. About 20% of SLE cases are diagnosed during childhood. However, because the majority of paediatric patients develop the disease during adolescence, it is rarely diagnosed in children under the age of five (1). The American College of Rheumatology (ACR) classification criteria from 1997 or the Systemic Lupus International Collaborating Clinics (SLICC) criteria from 2012 were employed to identify SLE. Although SLE is primarily considered a disease of women, its prevalence varies with age. The female-to-male ratio is 3:1 before puberty and 9:1 after puberty(1,2).

Childhood SLE (cSLE) is an uncommon disease with an incidence of 0.3 to 0.9 in every 100,000 children and a prevalence of 3.3 to 8.8 in every 100,000 children (3). This disease is reported to be more common among African Americans, Native Americans, Hispanics, and Asians (4-6). Non-white populations are two to four times more likely to have the disease, and it is more severe in men, children, and late-onset lupus (7). SLE's incidence and prevalence are much lower in children than in adults. In European and North American studies, the annual incidence of SLE in children (< 16 years old) was fewer than 1 per 100,000 (8). However, the genuine incidence and prevalence of cSLE in this region are still unclear due to the lack of statewide population- based epidemiological data.

The clinical course of cSLE is more severe and aggressive than that of adult SLE. As a result, children with SLE often require treatment with moderate- to high-dose steroids to manage disease progression.(2) Factors such as multi-organ involvement, disease severity, and long-term corticosteroid therapy have a massive impact on SLE patients and their families. Research by Nizam et al. measured the psychological problems in children with idiopathic nephrotic syndrome (INS) during corticosteroid therapy compared with healthy children (9). The researchers discovered significant differences in mean total CBCL scores between INS and healthy children, particularly in the withdrawn, somatic, anxiety, and aggressiveness subscale. A similar correlation was identified between the total number of psychological problems and corticosteroid dosage.

Healthcare providers for children and adolescents with SLE should consider strategies to support a child's physical and psychological development.

A local study by Ilias et al.(10) researched the sociodemographic influence, onset patterns, and outcomes of children aged under 15 years diagnosed with SLE that were admitted to a tertiary hospital in Malaysia. The majority of the subjects were female, and the most common clinical manifestations were haematological and renal findings.

cSLE, despite its dormant state, will still require disease surveillance and monitoring. The disease causes not only physical complications but also psychological effects. Factors including multiple hospitalisations, frequent disease monitoring and blood sampling, multiple medications, and restricted outdoor activities due to avoidance of sun exposure; all require psychosocial adaptation (11). Information on the prevalence of emotional and behavioural problems in cSLE patients is limited.

According to Saletra and Olesiska (12), negative emotions such as depression, despair, anxiety, guilt, and anger significantly worsen the quality of life (QOL) of SLE patients compared with the general population. Notably, many patients reported feelings of frustration, as well as a lack of confidence and control over their lives. The most commonly reported symptom was feelings of anxiety (70% of patients), followed by mood disorders (61.3% of patients), and then depression (50% of patients) (12).·

Louthrenoo et al.(13) discovered that, despite the challenges and difficulties, parents with cSLE reported mild emotional distress in their children with SLE. This may be due to the study being conducted while the children were in remission rather than during the active phase when it was poorly diagnosed with obvious neuropsychiatric symptoms (13). Nonetheless, children with SLE had lower overall social skills scores than the control group, indicating significantly impaired social functioning. Studies on psychological problems among the paediatric population are found to be scanty, especially in Southeast Asia.

Hence, the current study aims to illustrate socio-demographic data, common clinical manifestations and identify the psychological problems among cSLE populations as reported by their parents, specifically in Malaysia.

2.2

Section B

Study Protocol

2.2.1

Documents submitted for Ethical Approval

Dissertation proposal

School Of Medical Science

University Science Malaysia

Prepared in partial requirement fulfillment

For the Degree of Master of Medicine

(Paediatric)

2019/2023

CHILDHOOD SYSTEMIC LUPUS ERYTHEMATOSUS (CSLE) AND ITS PSYCHOLOGICAL IMPACT :

DUAL TERTIARY CENTRE EXPERIENCE

Protocol v2.0

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Research Title

Childhood Systemic Lupus Erythematosus (cSLE) and Its Psychological Impact : Dual Tertiary Centre Experience

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Introduction:

Systemic Lupus Erythematosus (SLE) is a chronic, relapsing-remitting, multisystem autoimmune disease that occurs in both children and adults. Approximately 20% of all patients who have SLE are diagnosed in childhood. The onset of SLE is rare in those younger than 5 years of age and most paediatric patients are diagnosed in adolescence. SLE is considered a predominantly female disease, and although most affected patients are female, the ratio changes with age. Prior to puberty, the female-to male ratio is 3:1 while after puberty, the ratio becomes 9:1. Beside that, there are marked racial differences observed in SLE. Native Americans are most susceptible to developing SLE, followed by African-Americans, Hispanics, Chinese, and Filipinos. The disease tends to be more severe in African-Americans and Hispanics.

SLE is a multigenic disease. A patient who has SLE is more likely to have a relative who has either SLE or another autoimmune disease such as thyroiditis or insulin-dependent diabetes. Epidemiologic, twin, and human leukocyte antigen data suggest a strong genetic contribution to the aetiology of SLE, but the exact cause is unknown. Multiple factors confer risk, including abnormalities in the metabolism of sex hormones, particular foods that have been found to be immunostimulatory in animals, and infectious agents. Overall, it has been suggested that an environmental trigger is necessary in a genetically predisposed individual to result in the disease.

Childhood lupus tends to be more severe at onset and has a more aggressive clinical course than adult lupus, therefore, children with SLE need a rather moderate to high dose of corticosteroid therapy to control their disease activity. The involvement of multiple organ systems and the chronicity of the disease, as well as its long-term treatment with corticosteroids, has had great impact on children and their families. Health care providers of children and adolescents with SLE should think about how to maintain the children’s physical and psychological development. In the natural course of the disease, medications alter physical appearance and information about possible outcomes in an important issue for children and their families.

Children with SLE need to be monitored for disease activity, even when the disease is inactive. They may be at high risk of psychological problems because of significant factors, including multiple hospitalizations, numerous physician visits, frequent laboratory monitoring and limitation of their activities, all of which require psychosocial adaptation.

Problem statement and study rationale

A number of different potential psychological problems can affect those with Systemic Lupus Erythematosus (SLE). Difficulties may arise from the disease process itself, which commonly affects the brain, or from the general effects of having a chronic long-term health condition. Depression and generalised anxiety can occur as a reaction to these symptoms and if the underlying lupus can be better controlled, features of low mood, loss of interest, and insomnia often improve. Owing to the high prevalence of psychological distress as stated in the study Prevalence of Mood and Anxiety Disorders in Women with SLE by A. Bachen et al , 65% received lifetime mood and anxiety disorder, and its contribution to symptoms of the disease, the identification of patients who are in need of adjunctive psychological treatment represents a significant clinical challenge.

In children, SLE is associated with significant morbidity consequential to their disease and treatment and comprises a wide-ranging spectrum of physical, functional, mental, and organ damage. Psychosocial implications of SLE in children are evident in the life disruptive responsibilities that the patient and their families must assume.

No local data is available to estimate the prevalence and associated factors in psychological problems in SLE patients, however the data from the literatures showed negative psychological outcomes in SLE patients developing countries.

Therefore, this study is intended to look at the psychological problems among Paediatric SLE patients using a validated questionnaire. We would like to further evaluate and provide early referral to Child Psychiatrist or Psychologist if necessary.

By using this questionnaire, we would help the parents/caretakers and treating physicians to understand and provide better support to SLE patients beside rapid meticulous control of disease activity.

Research Question :

1. What are the prevalence of psychological problems in Systemic Lupus Erythematosus (SLE) among the paediatric population?
2. What are associated factors for psychological problems in Systemic Lupus Erythematosus (SLE) among the paediatric population?

The objective of the study General:

To determine psychological problems in Systemic Lupus Erythematosus (SLE) patient among the paediatric population.

Specific:

1. To illustrate socio-demographic data and common clinical manifestation of children with Systemic Lupus Erythematosus (SLE).

2. To identify psychological problems in children Systemic Lupus Erythematosus (SLE) patient among paediatric population.

Study hypothesis:

Social demographic, anthropometric measure and related disease are associated factors for psychological problems in Systemic Lupus Erythematosus (SLE) among paediatric population.

Literature review

There has been limited published information regarding emotional and behavioural problems in children with SLE. A cross sectional study in Chiang Mai University Hospital, Thailand done by Louthrenoo et al. regarding Psychosocial functioning of children with systemic lupus erythematosus and was published in 2012. The objective of this study was to assess emotional and behavioural problems in children and adolescents with SLE during remission of disease activity.

The children were given 2 questionnaires including the Children Depression Inventory (CDI) and Multidimensional Anxiety Scale for Children (MASC). The parents completed the Child Behaviour Checklist (CBCL). They measured the internalizing, externalizing and total behavioural score and overall social competence in the SLE group and healthy control group. This study showed that parents reported low emotional problems in their children who had SLE. This may be explained by the timing of report, which is when the children were in remission and doing quite well comparing to during active disease, when many children were quite sick and had obvious neuropsychiatric symptoms. The overall social competence score of children with SLE was lower than that of the controls, indicating poorer social functioning. This finding is consistent with those reported by Moorthy *et al*. that children with SLE were impacted in their social relationship.

Moorthy et al. in the study Quality of life in children with systemic lupus erythematosus: a review published in 2007 mentioned that Quality of life (QOL) is a global, dynamic and personal construct, encompassing physical, psychological and social domain. Health-related quality of life (HRQOL), distinct from QOL and health status, is defined as “optimum levels of mental, physical, role and social functioning, including relationships and perceptions of health, fitness, life satisfaction and well-being”, incorporating the ‘assessment of patient’s satisfaction with treatment, outcome and health status and with future prospects. SLE is associated with significant morbidity consequential to their disease and treatment and comprises a wide-ranging spectrum of physical, psychosocial, and economic implications.

Ruperto et al. assessed HRQOL in 297 patients with SLE using Child Health Questionnaire (CHQ) and found the most affected CHQ subscales to be global health, general health perceptions and parent impact emotional. HRQOL was impacted by both disease activity and accumulated damage, especially in renal, CNS, musculoskeletal systems.

In a cross-sectional study of 24 children with SLE, physical function (Childhood Health Assessment Questionnaire-CHAQ) significantly correlated with Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (rho=0.4, p=0.04), SLICC Damage Index (SDI) (rho=0.6,p=0.004) and was associated with severity (p=0.03). HRQOL

(Pediatric Quality Of Life Inventory-PedsQL) did not significantly correlate with above parameters. Higher self-concept and socioeconomic status correlated (p<0.05) with better physical function and QOL.

Sliem et al. conducted study in Department of Internal Medicine, Faculty of Medicine, Suez Canal University, Egypt in 2010. It measures impact of the disease activity on the quality of life (QoL), a case control study involving 59 SLE Egyptian patients (mean age 28.6 years, 94.9% females) and 20 healthy controls was undertaken. Disease activity was measured by SLE Disease Activity Index (SLEDAI), and quality of life was measured by Short Form–36 health questionnaire (SF-36). As a results mucocutaneous and haematological manifestations were present in most of the patients

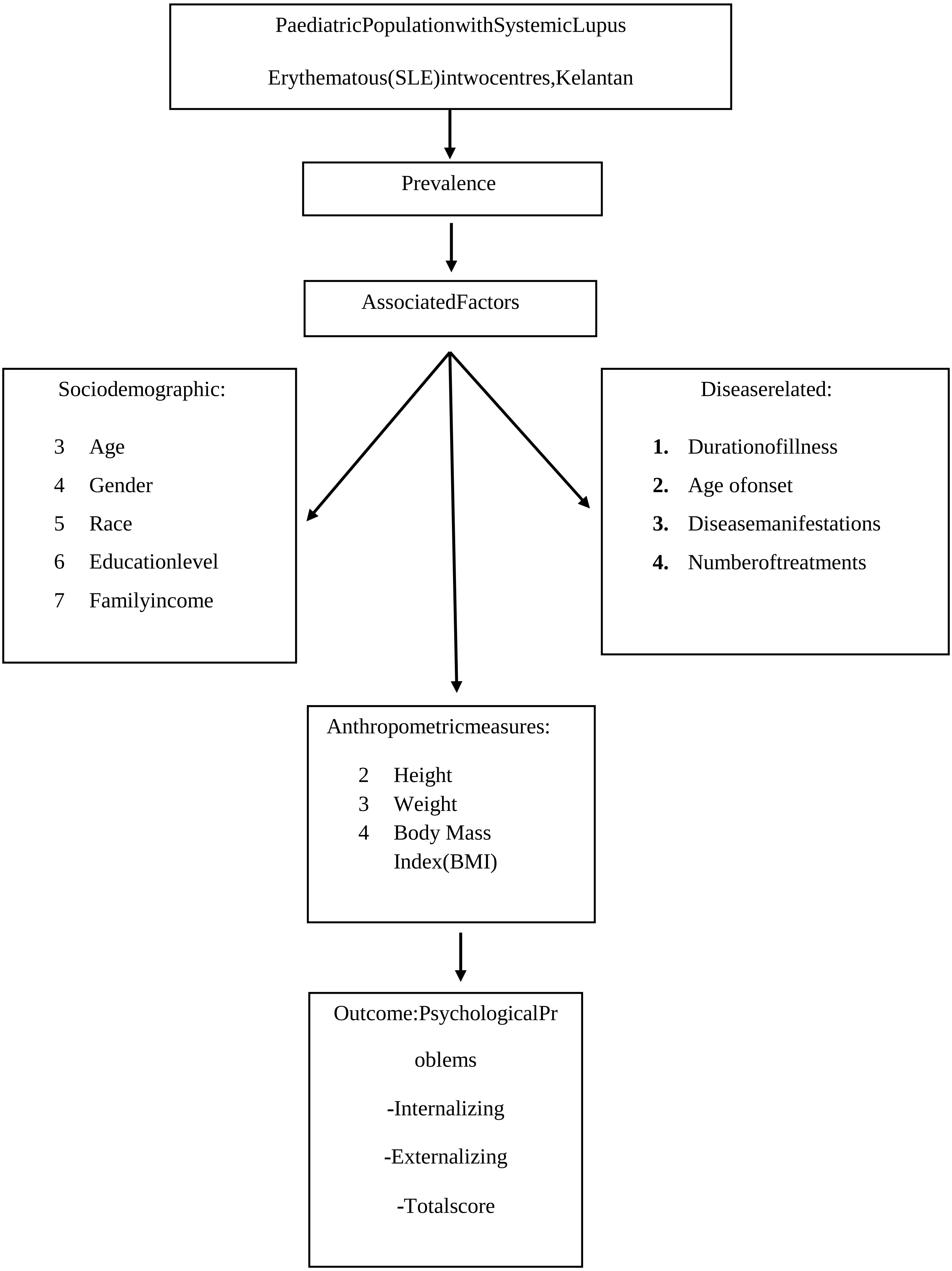
and arthralgia in half of them. All domains of SF-36 including general health, physical functions, physical limitations, energy/fatigue, emotional well-being, pain, social functions, and health changes were significantly lower in SLE patients compared to controls. Except for emotional limitations, all domains were correlated with disease activity and low in class IV-V lupus nephritis.

Olesińska and Saletra, from department of systemic connective tissues disease, national institute of geriatrics, rheumatology and rehabilitation, Warsaw, Poland published a review in Reumatologia 2018. Said that many studies show that quality of life in patient with SLE is lower than general population, independently of variable : measurement instruments (SF36,SF20,SF20+, and QOLS), ethnic origin or the size of the study group. It refers both, to the evaluation of physical and mental health. More than 2/3 of patients with SLE suffer from emotional disorders. The following were observed in the studies: feeling sad, depression, fear, anxiety, guilt, wrath. Many patients also experience the feeling of frustration and a lack of confidence, independence control over one's life.

Most frequent symptoms include feeling of anxiety reported by over 70% of patients, mood disorders in 61.3% as well as depression in 50% of patients. Anxiety is characterized by internal fear, lack of comfort and security. The feeling of anxiety appears already at the outset of the disease and can accompany patients with SLE throughout the life. Most of concerns result from unpredictable course of the disease and the prognosis. The intensification of emotional disorders is particularly present at the time of disease aggravation. The disease triggers the feeling of helplessness and exhaustion by everyday struggle that the patient cannot win.

Sometime symptoms of depression take form of somatic disorder : whole body pain, weight loss/gain, lack of interest in sex, amenorrhea and concentration and attention disorder.

Conceptual Framework:



Research design:

Prospective study

Study area:

Paediatric Nephrology Clinic Hospital USM and Hospital Raja Perempuan Zainab II, Kelantan.

Study duration:

March 2022-February 2023 (1 year)

Study population:

All paediatric population diagnosed with Systemic Lupus Erythematous (SLE) who attended to Paediatric Nephrologist clinic in Hospital Universiti Sains Malaysia (USM) and Hospital Raja Perempuan Zainab II, Kelantan

Subject

criteria Inclusion

criteria:

1. Parents/ caregivers who have children diagnosed with Systemic Lupus Erythematosus age 6-18 years old

1) Diagnosed or/and received treatment under Paediatric Nephrology Clinic Hospital USM and Hospital Raja Perempuan Zainab II

2. Diagnosed at least six months from the onset.

Exclusion criteria:

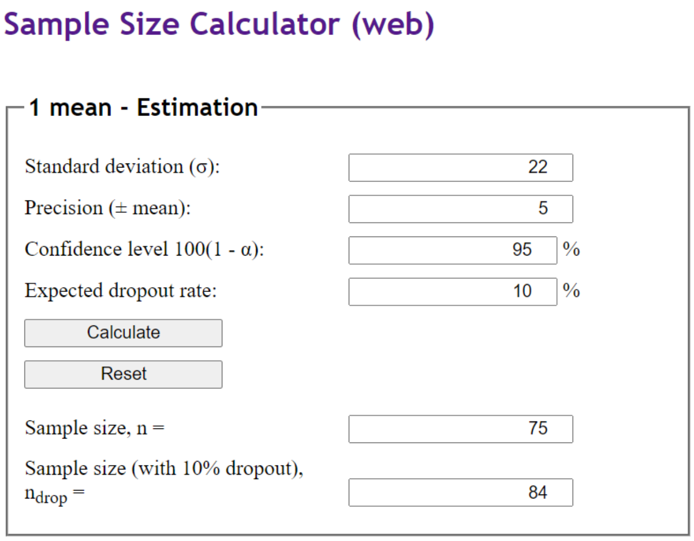
1. Paediatric SLE patients not consented to include in the research.

2. Paediatric SLE patients with confirmed neuropsychiatric involvement.

Sample Size Estimation:

To achieve the first objective, single mean estimation formula (Arifin W.N 2020) was used. The formula is shown as below:

Variable	SD	Precision	n	n+ 10%	Reference
Internalizing	7	3	21	24	Louthreno et al . (2012)
Externalizing	7	3	21	24	
Total Behaviour score	22	5	75	84	
Confidence level = 95% expected drop out = 10%					



Sample Size Calculator (web)

1 mean - Estimation

Standard deviation (σ): 22

Precision (± mean): 5

Confidence level 100(1 - α): 95 %

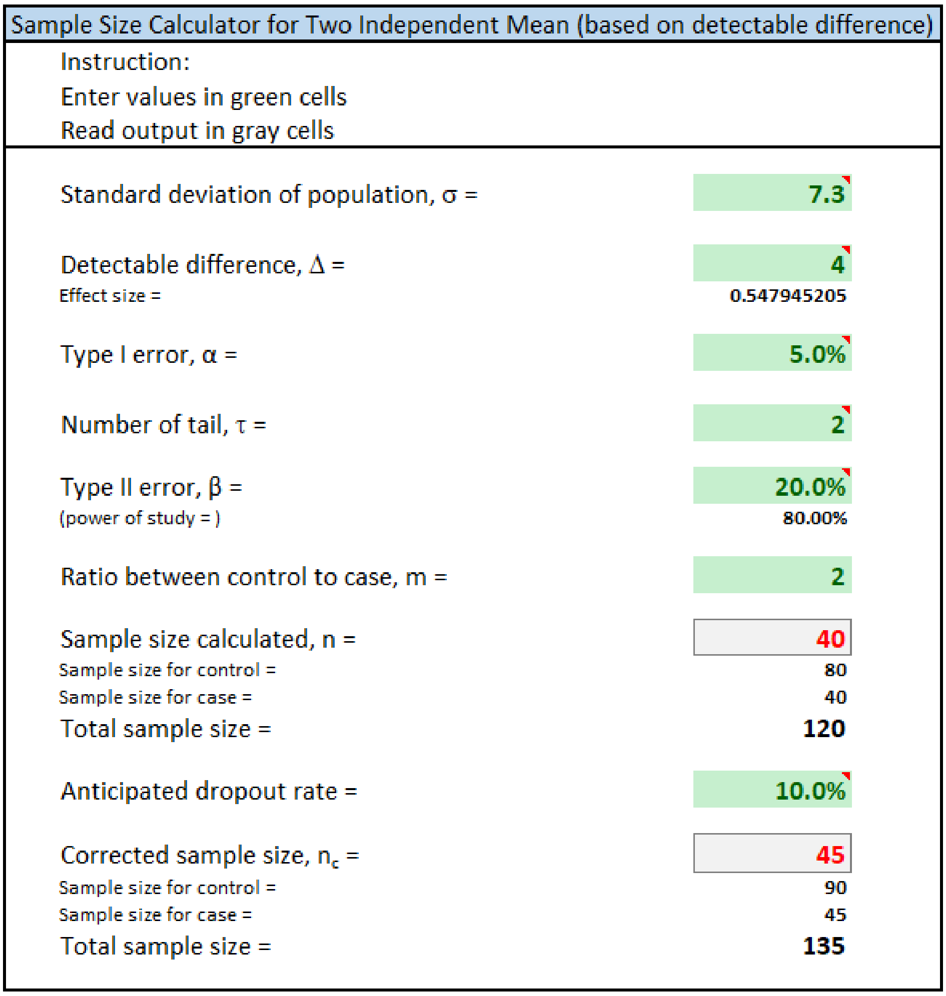
Expected dropout rate: 10 %

Sample size, n = 75

Sample size (with 10% dropout), n_{drop} = 84

To achieve the second objective, two independent mean will be used. The expected effect size was 0.55, with an α error of 0.05, a power of 0.8, a total of 10 predictors, and an estimated dropout or outlier rate of 10%.

The formula is shown as below:



Sample Size Calculator for Two Independent Mean (based on detectable difference)

Instruction:
Enter values in green cells
Read output in gray cells

Standard deviation of population, σ =	7.3
Detectable difference, Δ =	4
Effect size =	0.547945205
Type I error, α =	5.0%
Number of tail, τ =	2
Type II error, β =	20.0%
(power of study =)	80.00%
Ratio between control to case, m =	2
Sample size calculated, n =	40
Sample size for control =	80
Sample size for case =	40
Total sample size =	120
Anticipated dropout rate =	10.0%
Corrected sample size, n_c =	45
Sample size for control =	90
Sample size for case =	45
Total sample size =	135

Based on estimated sample size for the 2 objectives, minimal required sample size to achieve all the objectives are 90 sample for controls and 45 sample for cases.

Sampling method and subject recruitment

Sampling method that will be used in this study is non- probability sampling. The announcement will be made using a poster that will be available in The Paediatric Nephrology Clinic. All parents will be invited during their children's follow-up to join in the study. Parents who are interested will be given consent form and assent will be asked from the children before they are recruited in the study. After that, Childhood Behaviour Checklist for Age 6-18 years (CBCL 6-18) questionnaires will be distributed to the parents and they will start to answer under strict monitoring of PI. Duration of 15 to 20 minutes is required for them to complete the questionnaires. After finished answering, the questionnaires will be collected, and data will be analysed by the researcher.

Research Tool:

1. Data collection sheet and consent

Patient sociodemographic information will be collected in organised data collection sheet. Each patient will be given specific identification number on the top of the form. Parent consent form is provided to who is eligible for this study.

2. Childhood Behaviour Checklist for Age 6-18 years (CBCL 6-18)

This research uses validated questionnaire from Childhood Behaviour Checklist for Age 6-18 years (CBCL 6-18). The questionnaire was translated to Bahasa Melayu. 3 domain subscales will be tested in this study (anxious, withdrawn, somatic complaints, thought problems, attention, rule-breaking behaviour, aggressiveness). It was developed by The Achenbach System of Empirically Based Assessment (ASEBA) through decades of research and practical experience. I already have the licence from author to use this questionnaire.

The inter-interviewer and test-retest reliabilities of the CBCL item scores were supported by interclass correlation of 0.93 to 1.00 for the mean item scores obtained by different interviewers and for reports by parents on 2 occasions 7 days apart. The internal consistency of ASEBA competence scales was supported by Cronbach alpha coefficients of 0.63 to 0.79 on the CBCL. For the empirically based problem scales, Cronbach alphas ranged from 0.78 to 0.97 on the CBCL. The scale scores were quite stable over 12- and 24- month period for the CBCL.