PREVALENCE AND ASSOCIATED FEATURES OF PERIPHERAL NEUROPATHY IN A COHORT OF MALAYSIAN SYSTEMIC SCLEROSIS PATIENTS IN UMMC.

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THESIS SUBMITTED IN FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF INTERNAL MEDICINE.

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Dr.Tharshannia Balaikerisnan

TABLE OF CONTENT PAGE

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATION

PN	Peripheral neuropathy
SSc	Systemic sclerosis
TNS	Total neuropathy score
NCS	Nerve conduction study
MRSS	Modified rodnan skin score
dSSc	Diffuse systemic sclerosis
lSSc	Limited cutaneous systemic sclerosis
BMI	Body mass index
CTD	Connective tissue disease
PAH	Pulmonary arterial hypertension
ILD	Interstitial lung disease
IHD	Ischemic Heart Disease
GERD	Gastroesophageal reflux disease
ENA	Extractable nuclear antigen
MTX	Methotrexate
PPI	Proton pump inhibitor
H2b	Histamine receptors blocker
IVIG	Intravenous Immunoglobulin.
MMF	Mycophenolate mofetil
HCQ	Hydroxycholoroquine
MCV	Mean corpuscular volume
GAVE	Gastric antral vascular ectasia
PDE-5i	Phosphodiesterase type 5 inhibitor
ACE-i	Angiotensin-converting-enzyme inhibitor

ICD	Implantable cardioverter defibrillators
VT	Ventricular tachycardia
EF	Ejection fraction
ENF	Epidermal nerve fiber

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ABSTRACT

INTRODUCTION

Peripheral neuropathy in systemic sclerosis (SSc) is an under recognized clinical feature of unknown prevalence. Commonly this group of patients complains of distal paresthesia.The etiology of peripheral neuropathy is unclear with various pathomechanisms being postulated to cause peripheral neuropathy ranging from vasculopathy affecting the vasa nevorum, direct compression damage due to edema and fibrosis and anti- neuronal antibodies against the nervous system.

OBJECTIVE

The aim of this study is to determine the prevalence of PN in SSc patients and to identify the associated factors such as clinical features, disease markers, comorbidities and medications.

METHODOLOGY

All SSc patients seen at the University of Malaya Medical Centre were included. Demographic, clinical and laboratory data were obtained from medical records. Skin tightness was assessed using the Modified Rodnan Skin Scoring tool (MRSS). Clinical symptoms of peripheral neuropathy was assessed using the modified Total Neuropathy Score (TNS). Nerve conduction studies (NCS) were carried out on the upper and lower limbs. Neuropathy was defined as abnormal TNS (score of ≥ 2) together with abnormal NCS. A diagnosis of symmetrical polyneuropathy was made if there were abnormal NCS parameters in at least 2 nerves including the sural, while focal neuropathy was defined as abnormal NCS of a nerve other than the sural nerve (radial, median, ulnar, common

peroneal). Associated SSc features such as severity of skin fibrosis , presence of vasculitis and raynaud's were assesed in all patients.

RESULTS

A total of 82 SSc subjects were identified and 54 enrolled. Of the 54 subjects, the majority were females (50, 90.9%). Most were from the limited cutaneous subset (43,78.6%) while 11 (21.4%) were from diffuse cutaneous subset. Mean age was 56.18 (SD ±12.3) years. Mean duration of disease (non-Raynaud's disease onset) was 9.6 years (SD ± 8.18) (range of 1 year to 44 years) years. Out of 54 patients , 34 (62.9%) had Total Neuropathy Score (TNS) of ≥ 2. On NCS, 17 (31.5%) patients and 12 (22.2%) had findings of symmetrical polyneuropathy and focal neuropathy respectively. A total of 14 (25.9%) SSc patients were diagnosed to have symmetrical polyneuropathy (combined TNS ≥ 2 and symmetrical polyneuropathy). There was no correlation seen in SSc related disease markers such as skin fibrosis, Raynaud's or vasculopathy and SSc specific auto-antibodies.

CONCLUSION

The prevalence of peripheral neuropathy in our Malaysian SSc cohort is similar to other studies. There were no significant associations with disease markers suggesting polyneuropathy may be due to non-disease conditions.

1.0 BACKGROUND AND LITERATURE REVIEW

1.1 EPIDEMIOLOGY

Systemic sclerosis (SSc) is an autoimmune disease with a diverse clinical manifestation secondary to underlying fibrosis and autoimmunity. Its relative rarity with variable clinical manifestations, progression, and severity has been is a major constrain in studying the epidemiology. The annual incidence in the United States of about 20 cases per 1 million adults. However several studies have estimated the prevalence of SSc in the United States is around 242 cases per 1 million (Mayes et al., 2003) adults therefore the true prevalence is unknown. It is more commonly seen in female population than males. Those with this rare disease seem present in their third or fourth decade of life.

1.2 PATHOGENESIS

The aetiology and pathogenesis of SSc are poorly understood due to its scarcity. Genetic predisposition, environmental factors and immune activation system is believed to be a contributing factor in its manifestation (Sujau et al., 2015). Vasculopathy and tissue fibrosis are the result of autoimmunity, inflammatory process and other components of the regulatory cascades (Raja & Denton, 2015). Endothelin-1 (ET-1) is responsible for skin fibrosis therefore it is a vital mediator in the pathogenesis of SSc(Denton & Black, 2004). The inflammation is caused by infiltrates of perivascular macrophages which then triggers multiple inflammatory cells leading to activation of fibroblast and subsequently fibrosis. This trigger the initial cascade of events which later on attract multiple inflammatory cell types includingactivation of

fibroblasts leading to increased deposition of fibrous tissue (Sakkas, 2005). The activation of transforming growth factor- beta (TGF-beta), interleukin-4, platelet derived growth factor (PDGF), and connective tissue growth factor (CTGF) leads to changes in the extracellular matrix which results in fibrosis(Sakkas, 2005).

1.3 CLINICAL MANIFESTATION

2013 ACR/EULAR Classification Criteria for Scleroderma was developed by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR). Skin thickening of the fingers extending proximal to the metacarpophalangeal joints is sufficient for diagnosis of SSc however if that is not present there are 7 othercriteria(skin thickening of the fingers, fingertip lesions, telangiectasia, abnormal nailfold capillaries, interstitial lung disease or pulmonary arterial hypertension, Raynaud's phenomenon, and SSc-related autoantibodies)with varying scores [Table 1] . A score of 9 is classified as definite SSc. The clinical manifestation varies from cutaneous , vascular or internal organ manifestation.

Table 1. 2013 ACR/EULAR Criteria for SSc classification

ITEM	SUB-ITEM	SCORE
Skin thickening ofthe fingers of both hands, extending proximal to the metacarpophalangeal joints		sufficient criterion;9
Skin thickening of the finger *(only count the higher score)*	Puffy fingers Sclerodactly of the fingers (distal to MCP but proximal to PIP joints)	2 4
Fingertip lesions *(only count the higher score)*	Digital tip ulcers	2

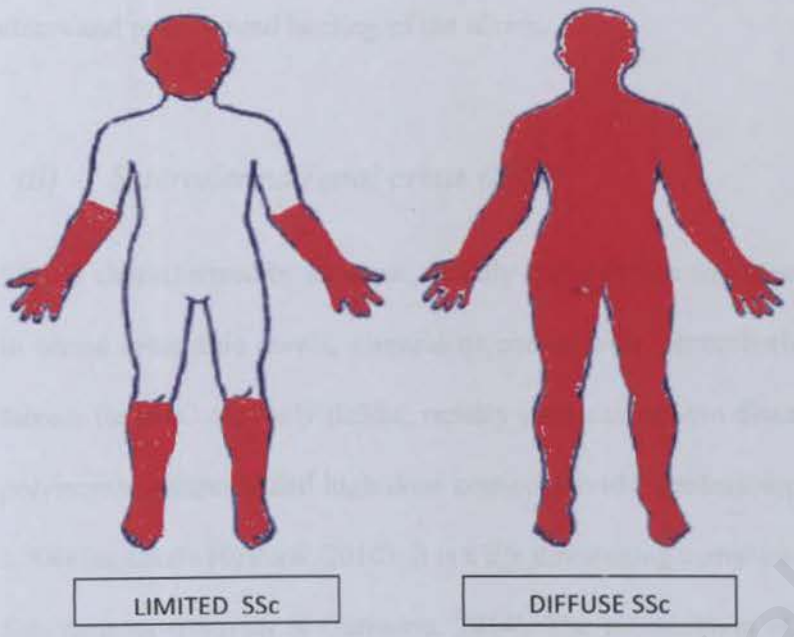
	Finger pitting scar	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension or interstitial lung disease *(maximum score of 2)*	PAH ILD	2 2
Raynaud's phenomenon		3
Systemic sclerosis-related autoantibodies *(maximum score 3)*	Anti-centromere Anti-topoisomerase Anti-RNA polymerase III	3

Patient with a score of $\geqslant$ 9 is definite systemic sclerosis. (van den Hoogen et al., 2013)

1.3.1 Cutaneous (Skin)

Pruritus and edema is the common complains seen in patients in the early phase of disease of cutaneous manifestation and subsequently hyperpigmentation (salt and pepper appearance). The fingers, hands and face are the earliest part of the body involved. There are 2 subsets: limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc).In lcSSc manifestation the skin tightening is limited to the distal forearms and knees and also the face. Diffuse subtype involves skin tightening proximal to the elbow and kneeswhich may extend to face, chest and abdomen. DcSSc patients are more prone to have internal organ fibrosis (Figure – 1) .

Figure 1.SSc clinical subsets (Johnson SR 1, Feldman BM et al, 2007)



1.3.2 Vascular

Vascular disease in SSc can extensively affect all vessels, commonly Raynaud's phenomenon, PAH and renal involvement.This is caused by inflammation and fibrogenic mechanism.

i) Pulmonary arterial hypertension (PAH)

Pulmonary hypertension (PH) in SSc is either due to primary PAH, pulmonary fibrosis or left ventricular disease(Sweiss et al., 2010). PAH in SSc is diagnosed by right heart catheterization with findings of pulmonary capillary wedge pressure of <15mmHg, pulmonary vascular resistance >3 wood unit withexclusion of thromboembolism and lung parenchymal disease.

ii) Raynaud's phenomenon

Raynaud's is an arterial vasoconstriction which is the most prominentvascular manifestation of SSc. It is defined as triphasic color changes of the finger precipitated by

cold, stress and change in temperature. This leads to chronic ischemia leading to digital ulcers and poor wound healing of the ulcers.

iii) Scleroderma renal crisis (SRC)

SRC is characterized by an acute, usually symptomatic increase in blood pressure, a rise in serum creatinine levels, oliguria or anuria with thrombotic microangiopathy. Risk factors for SRC are early dcSSc, rapidly progressive skin disease, presence of RNA III polymerase antibody and high dose corticosteroids, prednisolone >30 mg daily (Nadera J. Sweiss, Linda Hushaw, 2010). It is a life threatening complication that occurs in 10%of SSc patients (Bhavsar & Carmona, 2014). The introduction of angiotension converting enzyme inhibitor in 1980's (ACE-i) has drastically improved survival outcomes (Shanmugam & Steen, 2012).

1.3.3 Gastrointestinal

Gastrointestinal manifestation is evident in 90% of both SSc subtypes(9,10). Any part of the gastrointestinal (GI) tract can be affected in SSc ranging from dyphagia, heartburn, bloating, diarrhea, constipation, fecal incontinence, pseudobstruction and small bowel bacterial overgrowth. Esophageal dysmotility results in symptoms of gastroesophageal reflux disease (GERD) which subsequently results in dysphagia, bloating and heartburn.Chronic GERD causes esophagitis, stricture formation and subsequently leads to microaspiration. Angiodysplasia in the antrum of the stomach also known as gastric antral vascular ectasia (GAVE) ("watermelon stomach") is the most common cause for gastrointestinal bleed and anemia in these patients. In general, both upper and lower GI symptoms in SSc can lead to malabsorption and malnutrition especially in those with severe GI manifestations.

1.3.4 Interstitial lung disease (ILD)

The most prevailing symptom of ILD in SSc is shortness of breath and decrease in exercise tolerance. In early stages of fibrosis and alveolitis patients may be clinically asymptomatic.Anti –Scl- 70 antibodies is associated with diffuse skin manifestation and lung involvement among Ssc patients and results in poorer outcomes(11). The frequency of anti-Scl-70 antibodies in SSc with pulmonary fibrosis is about 45% (Hietarinta, Lassila, & Hietaharju, 1994; Mehra, Walker, Patterson, & Fritzler, 2013).Two main causes of death in SSc are ILD (33%) and PAH (28%) (Tyndall et al., 2010). A European Scleroderma Trials and Research group (EUSTAR) analysis revealed, in a cohort of 3656 SSc patients, that ILD is present in 53% of cases dcSSc and in 35% of cases with lcSSc (Tyndall et al., 2010).

1.3.5 Cardiac involvement

Primary cardiac involvement in SSc include pericarditis, pericardial effusion, myocardial fibrosis, heart failure, myocarditis, myocardial infarction (MI), conduction disturbances, and arrhythmias (Janosik et al., 1989).

1.3.6 Extra-cutaneous manifestation : Myositis, Arthritis, Calcinosis and Telangectasia

Extra-cutaneous manifestation in SSc patients are myositis, arthritis , calcinosis and telangectasia. Patients with Ssc may develop myopathy which primarily affect proximal muscle or present as myositis.Clinical features,histological and electromyographic features are similar to polymyositis or dermatomyositis(Ranque, Authier, Berezne, Guillevin, & Mouthon, 2007). Arthritis in SSc is more commonly seen in SSc overlap syndrome with rheumatoid arthritis.Telangiectasiaes are vasodilated post-capillary

venules commonly found on the face ,hand and mucosa.It is a manifestation of microvascular change in SSc patients The presence of telangiectasiaes is associated with the presence of pulmonary vascular disease (Shah, Wigley, & Hummers, 2010). Presence of calcinosis contributes to poor digital ulcer healing. Both longer disease duration and osteoporosis were independently associated with calcinosis (Pai & Hsu, 2017).

1.4 TREATMENT

Patients with SSc is treated symptomatically based on organ involvement. Low dose corticosteroids (prednisolone ≤15 mg daily) are used in SSc patients to control early skin or organ-based inflammation. Systemic immunosupressants are considered in patients with active diffuse skin involvement and in those with clinically significant ILD, myocarditis or with severe inflammatory myositis or arthritis. The table adapted below summarizes the key aspects of treatment for individual complications of SSc (Denton & Khanna, 2017).

Table 2. Treatment recommendations for major complications of SSc.

Clinical manifestation	Treatment	Studies	Level of evidence
Interstitial lung disease	Pulse Cyclophosphamide monthly then maintenance Azathioprine/MMF	SLS-I/ FAST	A
	MMF as first line therapy	SLS -II	A
	HSCT – in patient who failed immunosupressant	ASTIS/SCOT	A
Pulmonary arterial hypertension	PDE-5i ERA epoprostenol analogues	DETECT ARIES-E (ambrisentan) BUILD-2 trial (bosentan)	A
Systemic sclerosis renal crisis	ACE-i	Steen	C

Skin and musculoskeletal manifestation	MTX – for early diffuse skin manifestation	PRESS	A
	MMF	PRESS	B
	Glucocorticoids – low dose for tendon friction rubs		C
	Biologics – in cases of resistant arthritis		C
Gastrointestinal	PPI/H2 blockers/ antacids for all patients		B
	Antibiotics for SIBO		C
	Prokinetics for abdominal distension		C
	Parenteral nutrition for refractory weight loss		C
Digital vasculopathy	Calcium channel blocker PDE-5i for digital ulcer Epoprostenol for digital ischaemia		A A A
Cardiac	ACE–i for systolic dysfunction Diuresis for diastolic dysfunction Immunosuppression for myocarditis ICD for low EF / VT		C C C C
Other manifestations • Calcinosis / Pigmentary changes	Medical – Bisphosphonates/ Chelating agent Surgical excision Pigmentary changes using laser treatment		C C C

MMF, mycophenolate mofetil; HSCT, haematopoietic stem cell transplantation; PDE5-i, phosphodiesterase5-inhibitor; ERA, endothelin receptor antagonist;MTX, methotrexate; ACE-i, angiotensin converting enzyme inhibitor; PPI, proton pump inhibitor; SIBO, small intestinal bacterial overgrowth; ICD, implantable cardioverter defibrillator ; EF, ejection fraction; VT, ventricular tachycardia

(Table adapted from (Denton & Khanna, 2017).

1.5 BURDEN OF DISEASE

High burden of disease morbidity results in poor quality of life among SSC patients (Bruni, Raja, Denton, & Matucci-Cerinic, 2015). These cohort of patients experience symptoms of psychological distress as the results of body image and physical disfiguration, limitation in activities of daily living and social implication (Heinberg et al., 2007). Sexual health among SSc patient is another major implication of these debilitating disease. Erectile dysfunction(ED) is reported in 81% sexually active SSc male patients (Impens & Seibold, 2010). The cause of ED is hypothesized as vasculopathic and fibrotic changes. In female subjects, sexual dysfunction is due to decreased sensibility, decreased hand function, chronic pain, and vaginal dryness (Schouffoer et al., 2009).

1.6 PROGNOSIS OF SSC

The most prevalent cause of death among SSc patients is cardiopulmonary related, it ranges from 23% - 35% (Elhai, Meune, Avouac, Kahan, & Allanore, 2012; Hachulla et al., 2009; Mayes et al., 2003). It was reported that the SSc cohort has fourfold higher mortality ratio than general population (Shah et al., 2010). Survival rate of ILD patients, at 5 years, is more than 90%, but is much lower (38% at 9 years) if the patient is affected by dcSSc (Mayes et al., 2003). The 5 year survival in the modern era for PAH is 87%, compared with 51% for SSc-PAH patients(Rubenfire et al., 2013).

2.0 NERVOUS SYSTEM INVOLVEMENT IN SYSTEMIC SCLEROSIS

Nervous system involvement in SSc is presumptively uncommon however there has been many case series that has been reported in the past. These includes the peripheral nervous system (PNS) consisting of polyneuropathy, cranial, entrapment and autonomic neuropathies, brachial plexopathy, lumbosacral radiculopathy and less commonly the central nervous system(CNS) involvement.

2.1 Central nervous system involvement in SSc

Headache, seizures and stroke has been reported as an association and not pathogenic mechanism due to SSc(Goldberg, Duncan, & Winkelmann, 1978; Pal, Gibson, Passmore, Griffiths, & Dick, 1989). White matter hyperintensities in patients with SSc have been shown to be an early sign of CNS involvement that correlates with the presence of Raynaud's phenomenon(Heron et al., 1999) as well as with neuropsychiatric manifestations such as headache, seizure anddepression. In patients with SSc and cerebral vasculopathy , Terrier et al found convincing association between CNS vasculopathy with severe vascular complication such as PAH and renal crisis(Terrier et al., 2009). An increased risk of neurologic involvement is associated with the presence of anti-Scl-70 (anti-topoisomerase-I) and anti-U1-RNP; these antibodies are frequently found in patients with dcSSc and overlap syndromes (Hietarinta et al., 1994).

2.2 Peripheral Nervous System involvement in SSc

Prevalence of peripheral neuropathy in has been retrospectively reported in smaller studies involving 14 to 60 patients, ranging from 0.01% to 28 % (Frech et al., 2013; Gordon & Silverstein, 1970; Paik et al., 2016; Poncelet & Connolly, 2003; Sant & Murphy, 1994; Schady et al., 1991). These small studies and case reports investigating peripheral neuropathy in SSc used various methods of assessments and definitions of peripheral neuropathy, therefore the exact prevalence of peripheral neuropathy in SSc is unclear.

The observation of polyneuropathy in SSc has been made since 1954 (Christopher & Robinson, 1972; Corbo et al., 1993; Lee, Bruni, & Sukenik, 1984; Richter, 1954). Pure sensory polyneuropathy is the most frequently associated neuropathy in SSc (Poncelet & Connolly, 2003; Schady et al., 1991). Other patterns of peripheral polyneuropathies observed were mixed sensory and motor polyneuropathy and mononeuritis multiplex (Hietaharju, Jaaskelainen, Kalimo, & Hietarinta, 1993; Poncelet & Connolly, 2003). Poncelet et al concluded that peripheral neuropathy in SSc rather involved large and small fibers in a non–length-dependent manner instead of compression. The method of assessment included quantitative sensory testing (QST) which is a sensitive test in addition to clinical neurological examination and nerve conduction study (NCS) (Poncelet & Connolly, 2003).

It is unknown whether neuropathy in patients with SSc is a primary or secondary event. A few possible pathomechanisms contributing to peripheral neuropathy have been studied. Firstly, the hypothesis involvement of vascular dependent neuropathy due to vasculitis or vessel wall deterioration of the vasa nervorum.Nerve biopsy lesions had shown increased connective tissue and clusters of myelinated fibres as well as microangiopathic changes in the nerve (endoneurial, perineurial and epineurial) vessels(Bruni et al., 2015). Alterations of vasa nervorum with intima proliferation intima

and adventitia edema was also observed (Oddis, Eisenbeis, Reidbord, Steen, & Medsger, 1987). Less commonly, biopsy proven vasculitis and mononeuritis multiplex were seen in few cases (Dyck, Hunder, & Dyck, 1997; Oddis et al., 1987; Said, Lacroix-Ciaudo, Fujimura, Blas, & Faux, 1988). Secondly, a direct compression damage such as edema in the early phase of disease and fibrosis in the advanced stage of disease may induce pressure on the nerves (Cerinic, Marco Matucci et all n.d). Thirdly the presence of anti-neuronal antibodies has been linked to SSc suggesting an immune-mediated mechanism directed towards the nervous system (Hietaharju et al., 1993).

A few studies investigated and reported the presence of cutaneous nerve involvement in SSc, involving myelinated, unmyelinated sensory and autonomic nerve fibres (Badakov, 1992). In a more recent study by Provitera et al, none of the 11 patients complained of sensory disturbances. However, significant loss of epidermal nerve fibres (ENF) density was seen with correlation with dermal vasculature extension in both affected skin and apparently normal skin with more severity in the clinically involved skin (Provitera V, Nolano M, Pappone N, Girolamo C di, Stancanelli A, Lullo F, et al. 2005;).A follow-up study of immunohistochemical of cutaneous innervation was done whereby expansion of dermal vascular bed with significant increase in ENF density following prostacyclin analogue, Iloprost infusion. This finding suggests tissue oxygenation reverts axonal terminal degeneration, therefore small-fibre neuropathy in SSc is a reversible process induced by local ischemia (Provitera et al., 2007). Interestingly, ultrastructural modifications of PNS in the skin of SSc patients was studied based on morphological findings examined on transmission electron microscope and concluded that the peripheral nerve damage in SSc has been shown to evolve from the early to the advanced phase, especially in the diffuse subset (Manneschi et al., 2005).

i) Cranial neuropathies

Cranial neuropathies have been described in many case reports namely trigeminal, optic , oculomotor, trochlear, facial and glossopharyngeal nerve. The most commonly affected is trigeminal neuropathy occurring in 5 to 15 percent of patients (Farrell & Medsger, 1982). In a case series of 10 patients with SSc who developed cranial nerve involvement, trigeminal sensory neuropathy was seen in all patients, one glossopharyngeal nerve, 5 facial nerve weakness and 3 vestibularcochlear. It is hypothesized that this is due to microangiopathy and fibrogenesis may be a contributing factor for nerve compression (Teasdall, Frayha, & Shulman, 1980).

ii) Entrapment (focal) neuropathies

Entrapment neuropathies commonly carpal tunnel syndrome are seen in SSc (Lee et al., 1984; Lori et al., 1996; Machet et al., 1992). Others reported nerve involvements are ulnar neuropathy, posterior tibial neuropathy,ilioinguinal nerve entrapment and meralgia paresthetica (Teasdall et al., 1980). The presence of nerve entrapment had been decribed to be due to mechanical factors such as calcinosis(Chammas, Meyer zu Reckendorf, & Allieu, 1995; Thurman, Jindal, & Wolff, 1991). Presence of carpal tunnel syndrome and cubital tunnel syndrome were seen in 7 out of 10 symptomatic patients based on ultrasound imaging studies(Tagliafico et al., 2011). It is also postulated that tissue edema may cause peripheral nerve compression therefore entrapment neuropathy especially in the early phase of the disease.

iii) Autonomic dysfunction

SSc patients scan have significantly abnormal autonomic function affecting mainly the parasympathetic pathways. Microcirculatory impairment, abnormal oesophageal motility, and gastrointestinal dysfunctionin SSc may be attributed to autonomic dysfunction (Klimiuk, Taylor, Baker, & Jayson, 1988). The precise nature of the autonomic dysfunction is unclear. It is possible that there may be involvement of the vasa nevorum.

3.0 OBJECTIVES AND BASIS OF STUDY

1. To determine the prevalence of symmetrical peripheral neuropathy in a multiethnic Malaysian SSc cohort.
2. To identify associated factors that can predispose to symmetrical peripheral neuropathy in SSc.

3.1 EXPECTED OUTCOME

i) Frequency of peripheral neuropathy in SSc is expected to be 1%-26%

ii) Associated factors that predispose SSc to peripheral neuropathy may include skin fibrosis, vasculopathy and non-SSc related etiologies such as concomitant disease and medications.

3.2 HYPOTHESIS

Peripheral neuropathy is frequent up to 30% in Ssc contributing to the burden of disease. The occurance may be due to SSc-related etiology such as the presence of skin fibrosis or vasculopathy.

4.0 METHODOLOGY

4.1 STUDY DESIGN

Cross sectional study

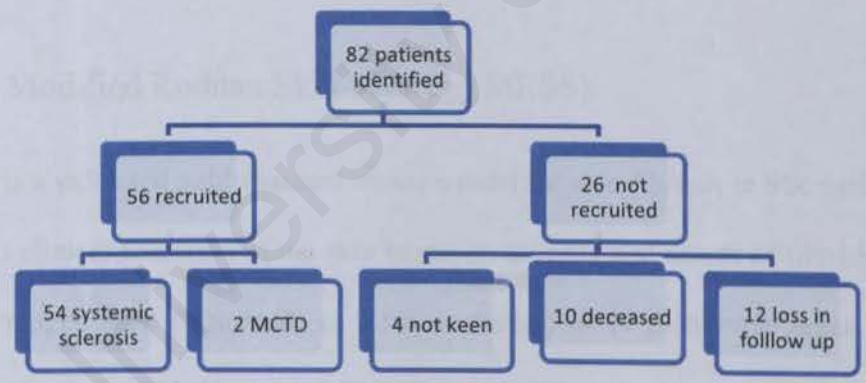
4.2 DURATION OF STUDY

January 2017 to August 2017

4.3 RECRUITMENT AND ENROLMENT

This study was approved by the University Malaya Medical Centre (UMMC) Medical Ethics committee [IRB reference number :20161227-4700] A total of 82 patients who fulfilled the 2013 ACR /EULAR (van den Hoogen et al., 2013) under UMMC Rheumatology clinic were identified based on the SSc database and 56 patients were recruited. Among 56 patients 2 patients had mixed connective tissue disease (MCTD) and were excluded from further analyses.

Figure 2. Flowchart of recruitment process



4.4 INCLUSION CRITERIA

All patients who fulfilled 2013 ACR/EULAR Classification Criteria for SSc and who gave written consent for participation.

4.5 EXCLUSION CRITERIA

Patients who refused to participate in the study and did not fulfill the ACR/EULAR criteria.

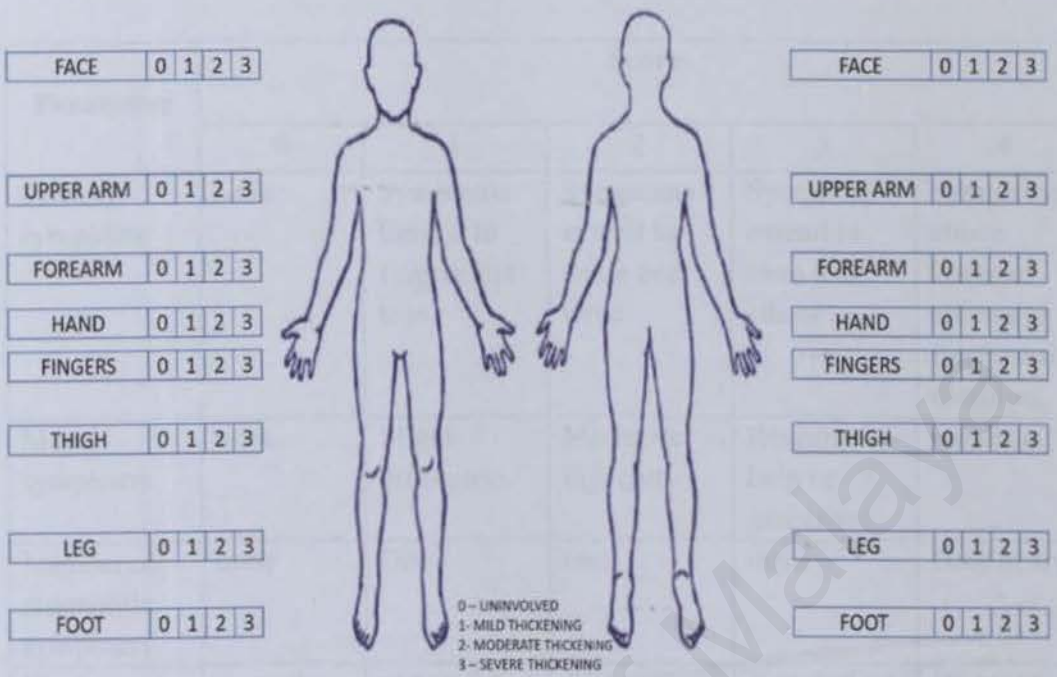
4.6 DATA COLLECTION AND QUESTIONNAIRE

Information on demographic data, clinical features, co-morbidities, laboratory tests results and medications were obtained from medical records. Patients were also interviewed on medical history and neuropathy symptoms. Full neurological examination was performed by the same investigator. This included muscle tone, power, tendon reflexes as well as sensory examination for pain using a 25g monofilament in the upper and lower limbs. Each component was scored based on a modified version of the Total Neuropathy Score (TNS).

a. Modified Rodnan Skin Scoring (MRSS)

MRSS is a validated gold standard measurement for skin fibrosis in SSc patients (Figure 3). It is clinical palpation of the skin based on severity and extent of fibrosis. The score values ranges from 0 (normal) to 3 (most severe) in 17 distinctive areas with a total maximum score of 51. However MRSS is not sensitive to measure early skin changes.

Figure 3. Modified Rodnan Skin Scoring Diagram (Clements et al 1993)



b. Modified Total Neuropathy Score (TNS)

The total neuropathy score is a validated tool to measure peripheral nerve function (Cavaletti G, Frigeni B et al 2007). Patients were screened for peripheral neuropathy using a modified Total Neuropathy Score that encompassed signs, symptoms and objective testing. For this study, two components based on symptoms were assessed: sensory and motor. Sensory symptoms including pin sensibility, paresthesias (tingling), numbness and neuropathic pain (burning,aching and stabbing) were assessed. In this study patients who had TNS score of ≥ 2 were labeled as having clinical neuropathy.

Table 3. Modified Total Neuropathy Score

Parameter	Score				
	0	1	2	3	4
Sensory symptoms	none	Symptoms limited to fingers and toes	Symptoms extend to ankle and wrist	Symptoms extend to knee and elbow	Symptoms above knees or elbows or functionally disabling
Motor symptoms	none	Slight difficulty	Moderate difficulty	Requires help or assistance	paralysis
Number of autonomic symptoms	none	One	two	three	Four or five
Pin sensibility	normal	reduced in fingers and/ or toes	Reduced up to wrist and / or ankle	Reduced up to elbow and / or knee	Reduced above elbow and/ or knees
Strength	normal	Mild weakness	Moderate weakness	Severe weakness	Paralysis
Tendon reflex	normal	Ankle reflex reduced	Ankle reflex absent	Ankle reflex absent, others reduced	All reflex absent

c. Nerve conduction study (NCS)

NCS provides accurate measurement of the functional status of sensory and motor fibres. Therefore the inclusion of NCS in assessment of peripheral neuropathy increases the specificity of the diagnosis. The most precise diagnosis of peripheral neuropathy incorporates clinical symptoms, signs and electrodiagnostic findings. All patients underwent NCS conducted by a consultant neurologist Prof Goh

Khean Jin and senior medical lab technician Madam Letchumy Ramanaidu. NCS was done over the right upper and lower limb. In the event the right side NCS could not recordable then the left side was studied. Skin temperature was kept at least at 32 degrees Celcius during NCS. NCS was carried out on Medelec synergy electromyography machine (Natus Neurology Inc, USA). Surface stimulating and recording electrodes were used in this study. During the test, the nerve is stimulated using electrodes that is attached to the skin, over the location of the nerve. One electrode stimulates the nerve while the other records the reading. The speed is calculated by measuring the distance between 2 electrodes and the time taken for the electrical impulse to travel between electrodes.

The following parameters were studied :

i) Sensory nerves : median , ulnar, radial, sural

ii) Motor nerves: median , ulnar, peroneal and tibial nerves

iii) F waves : median, ulnar , peroneal and tibial nerves

Normal values for our laboratory were obtained previously and abnormal values were defined as < 1st or > 99th percentile of the normal range of values (England MD, J.D & Gronseth et al , 2009).

d. Laboratory testing

Laboratory results were obtained. This included

i) Full blood count, renal and liver profile, fasting blood sugar (FBS), HbA1c

ii) Inflammatory markers - erythrocyte sedimentation rate (ESR), c-reactive protein (CRP) , fasting blood sugar (FBS), HbA1c

iii) Immunological markers – dsDNA, anti-nuclear factor (ANA), extractable nuclear antigen (ENA)

e. Diagnosis

A diagnosis of peripheral neuropathy was defined as presence of clinical neuropathy and abnormal NCS following the American Academy of Neurology (AAN) definition for clinical research (England MD, J.D & Gronseth et al (2009). In this study, symmetrical polyneuropathy was defined by a modified TNS score of ≥ 2 with abnormal NCS parameters in at least 2 nerves including the sural nerve. Focal neuropathy was defined as abnormal NCS parameters in only 1 nerve without sural involvement.

4.7 STATISTICAL ANALYSIS

Descriptive analyses of all the demographic variables were performed using IBM SPSS software version 24. Continuous variables were described with mean and standard deviation. Categorical variables were reported in frequency and percentage. Clinical associations with peripheral neuropathy were evaluated using Pearson chi-square, Fisher exact, student t-test and non-parametric test, where appropriate.All mean differences were reported with its corresponding 95% Confidence Interval (CI). A P value of less than 0.05 was taken as statically significant.

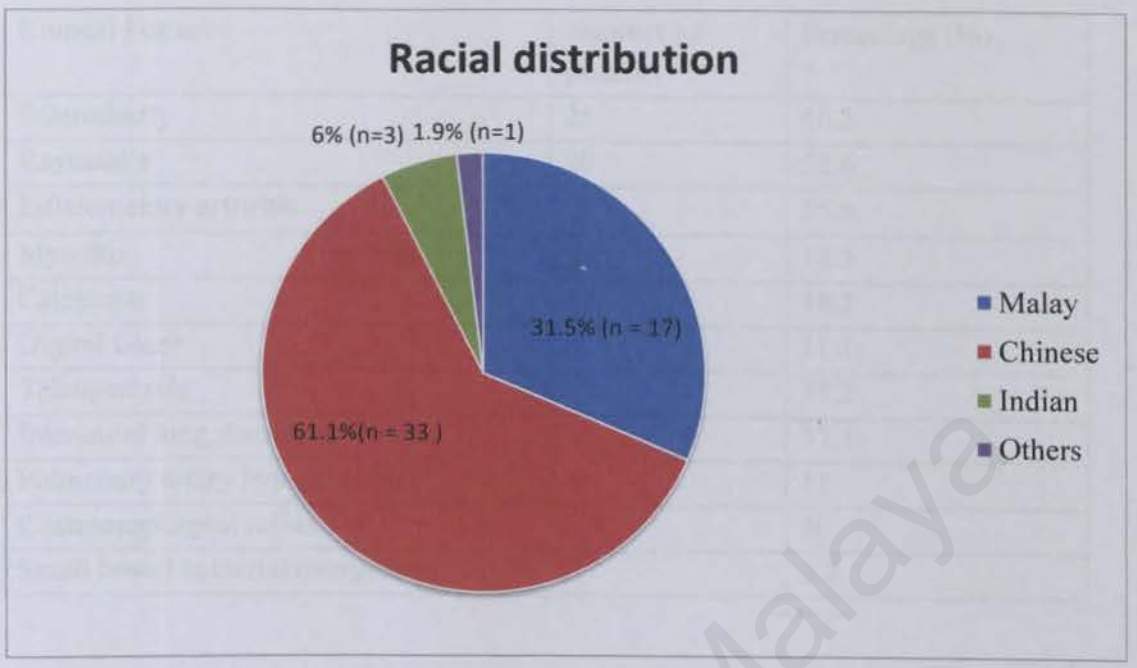
5.0 RESULTS

A total of 54 patients fulfilling the ACR/EULAR criteria for SSc were recruited into this study. 33 (58.9%) patients had TNS score of $\geqslant 2$. There were 24 (42.9%) patients who had abnormal NCS, 17 (30.4%) patients with NCS symmetrical polyneuropathy.A total of 14 (25.9%) were diagnosed as symmetrical polyneuropathy (based on combined clinical and NCS criteria). We mainly analysed patients with symmetrical polyneuropathy.

5.1 Demographic data

The mean age of our patients was 56.18 (SD ±12.3) years with range of 20 to 84 years. The majority were females (n = 50, 90.9%) The ethnic breakdown was as follows with majority being Chinese (n = 33, 57.9%) , Malays (n = 17, 29.8%) , Indians (n = 3, 5.3%) and others (n=1, 1.8%) (Figure 4.1). The mean duration of disease ranged from 1 to 44 years with mean duration of 9.6 (SD ± 8.18) years.

Figure 4. Race distribution among SSc patients



5.2 Clinical manifestation of SSc

Majority of patientshad limited cutaneous subtype (n= 44, 78.6%) while the others had diffuse cutaneous subtype. (n = 12, 21.4%). Among these subgroups of patients, (n=12, 21.4%) had overlap syndrome with other CTDs such as Sjogren's, systemic lupus erythematosus(SLE) and rheumatoid arthritis. The frequency of various clinical and immunological manifestation of SSc are listed in the chart below (Figure 4.2) The 3 most common clinical manifestations were inflammatory arthritis(n=30, 55.6%) followed by Raynaud's (n=30, 55.6%) and sclerodactyly (n=25, 46.3%). As for organ manifestation ILD (n =31, 57.4%) and GERD (n = 27, 50%) were the most commonly seen.

Table 4. Clinical features of SSc

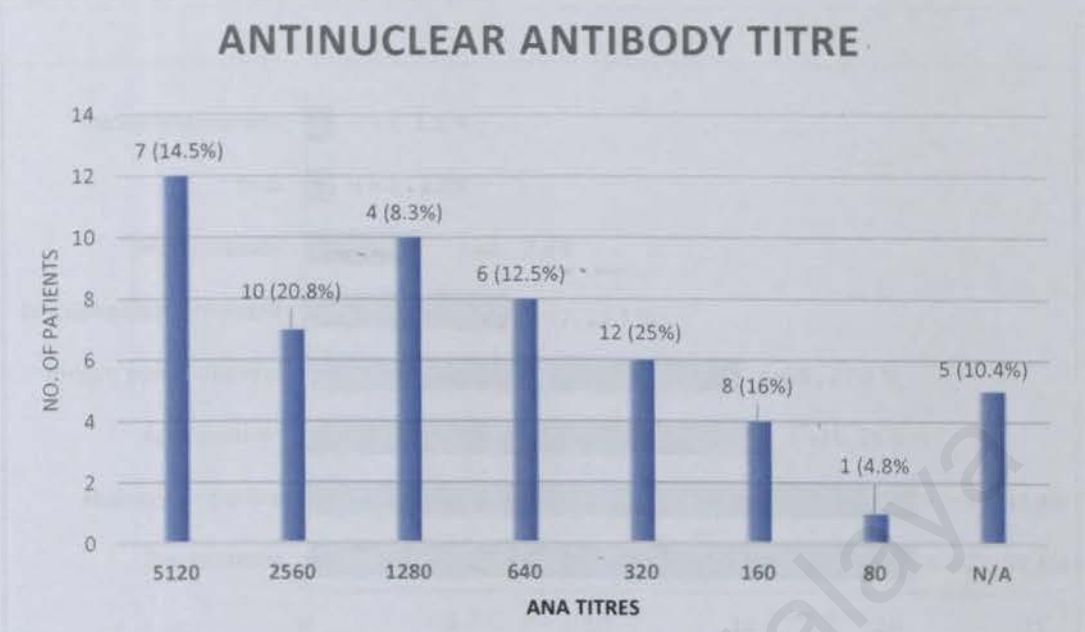
Clinical Features	Number of patients	Percentage (%)
Sclerodactly	25	46.3
Raynaud's	30	55.6
Inflammatory arthritis	30	55.6
Myositis	10	18.5
Calcinosis	10	18.5
Digital Ulcer	6	11.1
Telangectasia	19	35.2
Interstitial lung disease	31	57.4
Pulmonary artery hypertension	5	11
Gastroesophageal reflux	27	50
Small bowel bacterial overgrowth	2	3.7

5.3 Immunological parameters

Positive ANA with strong titres were present in majority of our SSc patients. Figure 5 and 6 below shows the specific SSc antibodies and the ANA titres in our SSc cohort.

Figure 5. Specific SSc autoantibodies in SSc patients

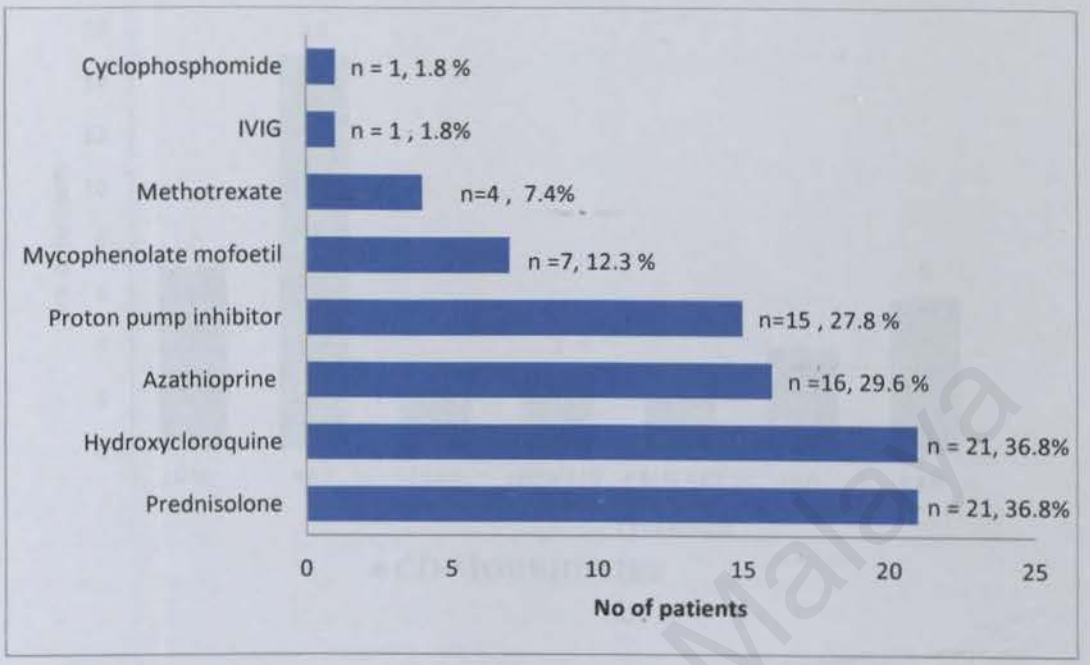
Figure 6. ANA titre for SSc patients



5.4 Medications

A majority of the Ssc patients recruited were on low dose prednisolone of less than 15 mg daily (n=21, 38.2%), followed by immunosuppressants azathioprine (n=16, 29.6%), hydroxycholoroquine (n= 20, 36.4%), mycofenolate mofetil (n=7, 12.7%) and methotraxate (n=4, 7.3%). There was one patient each who received cyclophosphomide few years ago and intravenous immunoglobulin (IVIG).

Figure 7. Current and past medications.

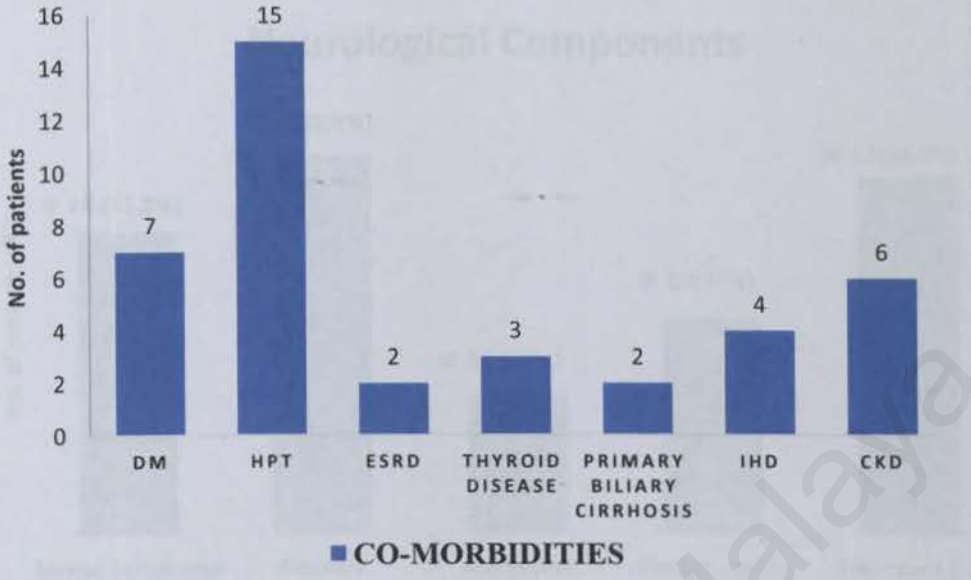


5.5 Comorbidities

The most common comorbidities seen were diabetes mellitus and hypertension.

However no significant association with PN and co-morbidities seen.

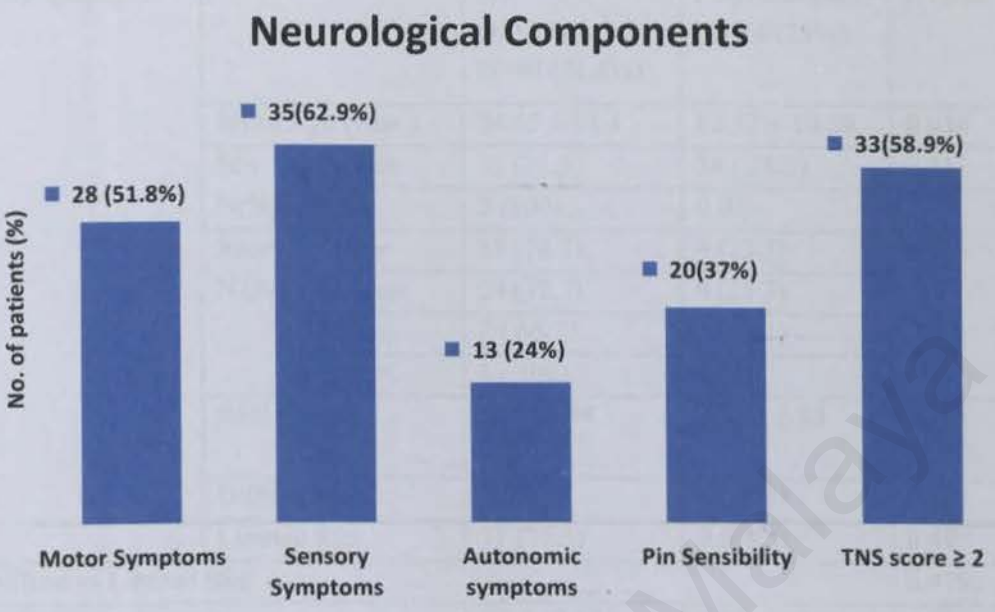
Figure 8. Underlying comorbidities in SSc patients



5.6 Neurological manifestation of SSc

The most common presenting complain among SSc patients were numbness of hands and feet. This is followed by muscle weakness and subsequently autonomic symptoms. There were 33 (58.9%) patients who had a modified TNS score of ≥2, and therefore had clinical neuropathy.There were 24 (42.9%) patients who had abnormal NCS, 17 (30.4%) patients with NCS symmetrical polyneuropathy and 12 (21.4%) patients with NCS focal neuropathy [3(5%) had overlap of both while 2(3%)patients neither had the above].33 (58.9%) patients had TNS score of ⩾2. A total of 14 (25.9%) were diagnosed as symmetrical polyneuropathy (based on combined clinical and NCS criteria).

Figure 9. Neurological characteristics with individual components of TNS assessment in SSc patients.



Symptoms were assessed based on TNS. Pin sensibility was done with 25g monofilament.

Table 5. List of focal neuropathies in SSc patients

Focal neuropathy	No. Of patients
Carpal Tunnel Syndrome	4
Peroneal neuropathy	5
Tibial neuropathy	1
Lumbosacral radiculopathy	2

Table 6. Comparison on clinical characteristics between those with and without polyneuropathy.

Demography			No polyneuropathy N=40 (71.4%)	Polyneuropathy N= 14 (25%)	P value
	Mean Age (y.o±)		54.65 ± 12.4	62.57 ± 10.69	**0.038**
	Sex N(%)	Female	35 (71.5)	14 (28.5)	0.311
		Male	5 (100)	0 (0)	
	Race N (%)	Malay	13 (76.5)	4 (23.5)	0.915
		Chinese	24 (72.7)	9 (27.3)	
		Indian	2 (66.7)	1 (33.3)	
		Others	1 (100)	0 (0)	
	BMI (mean)		22.9±5.94	21.0 ± 5.13	0.991
	Diffuse SSc		9 (22.5)	4 (28.5)	0.722
	Limited SSc		31 (77.5)	9 (64.2)	0.490
Diffuse vs Limited SSc					0.479
MRSS score (mean)			9.6 ± 8.17	8.36 ± 4.23	0.615
SSc duration (mean)			9.85 ± 8.94	8.00 ± 5.51	0.255
Hemoglobin (mean) (g/L)			12.3 ± 1.35	11.2 ± 1.25	**0.009**
MCV > 97 (fl)			4 (10)	3 (5.5)	0.337
Creatinine (mean) (umol/L)			61.9 ± 53.1	154 ± 260	**0.037**
Fasting blood sugar (mean) (mmol/L)			4.32 ± 1.99	5.67 ± 2.46	0.259
ESR (mm/hr)			34.5 ± 20.7	44.23 (19.6)	0.587
SSc specific autoantibodies N (%)	RNP		11 (27.5)	4 (28.5)	0.858
	SSA		10 (25)	2 (14.2)	0.707
	SSB		8 (20)	1 (7)	0.968
	SCL-70		14 (35)	4 (28.5)	0.763
	Ro-52		4 (10)	3 (21.4)	0.972
	Jo-1		3 (7.5)	2 (14.2)	0.823
	Anti-Smith		3 (7.5)	2 (14.2)	0.823
	Anticentromere		3 (7.5)	1 (7)	1.000
	PMscL100		6 (15)	3 (21.4)	1.000
	RP155		2 (5)	1 (7)	1.000
	RP11		0	1 (7)	0.333
	Fibrillin		3 (7.5)	3 (21.4)	0.464
Comorbidities N (%)	DM		4 (10)	3 (21.4)	0.358
	HPT		10 (25)	5 (35.7)	0.498
	CKD		4 (10)	4 (28.5)	0.080
	IHD		1 (2.5)	3 (21)	0.049
	Thyroid disease		2 (5)	1 (7)	1.000
Clinical features N (%)	Sclerodactly		19 (47.5)	6 (42.8)	0.764
	Digital Ulcer		4 (10)	8 (57.1)	0.643

	Raynaud's	21 (52.5)	9 (64.2)	0.520
	Inflamatory arthritis	22 (55)	8 (57.1)	0.890
	Myositis	7 (17.5)	3 (21.4)	0.708
	Telangectasia	14 (35)	6 (42.8)	0.749
	Calcinosis	7 (17.5)	3 (21.4)	0.708
	ILD	20 (50)	12 (85.7)	0.270
	GERD	19 (47.5)	8 (57.1)	0.757
	PAH	4 (10)	1 (7)	1.000
	SIBO	1 (2.5)	1 (7)	0.455
Treatment N (%)	Azathioprine	13 (32.5)	3 (21.4)	0.515
	Prednisolone	16 (40)	5 (35.7)	1.000
	MTX	4 (10)	0 (0)	0.338
	MMF	5 (12.5)	2 (14.2)	1.000
	HCQ	16 (15)	5 (35.7)	1.000
	PPI	13 (32.5)	2 (14.2)	0.302
	IVIG	1 (2.5)	0 (0)	0.259
	CYC	0 (0)	1 (7)	0.259

Values are presented in ± SD or the number (%) unless indicated otherwise

Table 7. Multivariate linear association in logistic regression

Variable	Odds ratio	CI	P value
Age	1.061	0.988-1.139	0.103
Haemoglobin (g/L)	0.588	0.338-1.021	0.059
Creatinine (umol/L)	1.004	0.999-1.010	0.117

(The odd ratio was adjusted to the variables mentioned above)

Associated factors with SSc-related polyneuropathy

On bivariate analyses, there were significant association between SSc polyneuropathy and age, haemoglobin and creatinine. Patients with polyneuropathy were significantly older and had lower mean haemoglobin level and higher mean creatinine levels than those without polyneuropathy. Logistic regression analysis, when including age, haemoglobin and creatinine levels as covariates, there were no significant association. However there was a trend towards lower haemoglobin (OR 0.588, 95% CI 0.338-1.02).

6.0 DISCUSSION

PN is an under recognised prevailing condition in autoimmune diseases.The frequency of PN among general population is estimated to be around 2.4% (Knupp-Oliveira & Cerinic, 1999). A study pubslihed by Sim et al reported 33% of rheumatoid arthritis patients had peripheral neuropathy (Sim, Kim, Yoon, Park, & Kim, 2014), while another study by Jasmin et al in a cohort of SLE patients reported 25% (Jasmin, Sockalingam, Ramanaidu, & Goh, 2015) and in primary Sjogren's syndrome was 27 % (Goransson et al., 2006). The frequency of PN among SSc patient is higher than general population ranging from 0.1% to 28 % (Frech et al., 2013; Gordon & Silverstein, 1970; Schady et al., 1991). The rarity of the disease is a major limitation in conducting studies among SSc patients. The prevalence of PN among Asian SSc population is not known and to our knowledge no such studies has been done to date.

This cross sectional study was carried out to meticulously assess prevalence of PN among SSc patients. The prevalence of PN mostly involving small sample size of SSc patients ranged between from 0.01% to 28 % (Gordon & Silverstein, 1970; Paik et al., 2016; Poncelet & Connolly, 2003). However not all studies assessed peripheral neuropathy in SSc by using NCS, and therefore with varying method of assessments and definitions of PN, the prevalence varied. A systemic review concluded that peripheral sensorimotor PN was present in 14.5% of SSc patients and hence is one of the most frequent PNS involvement in SSc (Berth Jones, 1990).

Peripheral neuropathy can be defined in many ways including physical signs, patient symptoms and diagnostic test results (Christopher & Robinson, 1972; Paik et al., 2016). In a recent study by Paik et al , PN was defined as positive TNS and or reduced sural amplitudes on NCS (Paik et al., 2016). Both parameters were used in effort to capture neuropathy affecting small and large fibers; whereas in our study, we defined

polyneuropathy as positive TNS score and abnormal electrophysiological parameter in at least 2 nerves including at least 1 sural nerve, which is accordance to the American Academy of Neurology consensus (England MD & Goransson et al., 2006). In our study the prevalence of SSc definite symmetrical polyneuropathy was 25.9%. This finding is similar to previously reported studies (Knupp-Oliveira & Cerinic, 1999; Paik et al., 2016; Schady et al., 1991).

In sensory nerve damage, patients often present with tingling sensation or numbness, loss of pain sensation and temperature, loss of co-ordination and burning or shooting pains which is worse at night. In motor neuropathy, patient often suffers from muscle weakness, twitching or even paralysis. These symptoms are very debilitating for a patient. The majority of our SSc patients presented with sensory symptoms mainly distal paresthesia or numbness compared to motor and autonomic symptoms, which had been well described and reported in other studies (Nolano et al., 2017; Poncelet & Connolly, 2003). These symptomatic patients may have cutaneous nerve involvement despite having no large nerve fibre involvement on NCS, indicating presence of small nerve fibre neuropathy (Manneschi et al., 2005; Provitera et al., 2007). The mechanism of neuropathy in SSc is not clear.

A study by Provitera V et al suggested small caliber unmyelinated nerve fibers were prominently affected in patients that had vascular bed changes suggesting ischemia. The same author subsequently reported in a follow up study that Raynaud's phenomenon was associated in increase of intraepidermal nerve fiber density suggesting it may be a reversible process (Provitera et al., 2007). Nerve biopsy will provide a valuable insight on the pathomechanism of PN in SSc. Prevalence of raynaud's in asian population is less commonly seen due to the tropical weather.

There were 12 (22.2%) SSc patients with focal neuropathy in our study. We did not include patients with focal neuropathy in our definition of peripheral neuropathy as the former may be due to compression or entrapment neuropathy. None of our patients complained of pain or presented acutely to suggest underlying immune mediated compression (i.e.vasculitis). The pathophysiology of focal neuropathy is not clearly understood; immune or vascular etiology will not only affect one nerve hence this may be related to distal nerve ischemia or compression due to edema or adjacent structures (Kowal-Bielecka et al., 2017) , (Cerinic MM, 1996).

Age was a noteworthy factor in our cohort of SSc patients. This findings correlates with the general population, The National Health and Nutrition Examination Survey (NHANES) found that 2873 patients with age above 40 , 8.1% had PN while those above 80 was 34.7% (Greg EW et al, 2004). There were a variety of contributing factors that may predisposed older patients to PN, ranging from comorbidities to nutritional deficiencies.

We also investigated whether higher creatinine levels were associated with PN in SSc; we found only 4 out of 8 SSc patients with CKD had evidence of polyneuropathy. There are many possible factors that may predispose chronic kidney disease (CKD) patients in general to PN such as uremic neuropathy, anemia and nutritional deficiencies (Arun V. Krishnan, 2009).

There was a trend towards significance for lower haemoglobin level which may suggest that anemia might be an independant factor to predict PN among SSc patients. In SSc patients anemia is commonly caused by occult GI bleeding, malabsorption, malnutrition or small bowel bacterial overgrowth. None were known to have peptic ulcer disease or GAVE . Low iron levels and vitamin B12 deficiency can predispose patients to PN however the former is reversible. In vitamin B12 deficiency damaged nerve may not be reversible despite adequate treament. In our cohort of patients, no correlation was seen

between high MCV and PN to suggest that our patients might have had vitamin B12 deficiency. However, serum vitamin B12 was not measured in all patients. Eventhough PN was more frequently found in patients with older age (p= 0.038), anemia (p =0.009) and higher creatinine levels (p =0.037) no significant association was found for SSc after adjustment for the above covariates on multivariate analysis as we had only 54 patients.

A recent publication by Paik et al with an equivalent number of patient to our study, reported that 82% of SSc patients had non-SSc related PN such as diabetes mellitus (17.7% vs 0, p =0.02) which was the main factor for the development of PN (Paik et al , 2016). Only 3 patients from this study had unknown reason of PN compared to all of our SSc patients, where presence of any of the comorbidites did not play a role in our study. Our study obtained the findings of polyneuropathy based on a more stringent and precised definition in accordance to the AAN recommendations compared to the study by Paik et al and other few studies (Hietaharju et al., 1993; Lee et al., 1984; Poncelet & Connolly, 2003), whereby in these studies subjects with neuropathic symptoms but normal NCS were also included. Despite this criteria and a small sample size, the prevalence of PN in our SSc cohort is similar to previous studies. Paik et al also found that PN was significantly present in their African American subjects. Our patients were predominantly Chinese (n=35, 72.7%), however no differences were seen among the three main Malaysian ethnic groups in terms of SSc polyneuropathy.

Our study demonstrates that PN was seen in 14 out of 54 patients (26%), none was directly related to SSc. Presence of Raynaud's phenomenon did not predispose SSc patients to PN. Effects of vasa nervorum leading to peripheral neuropathy is unclear. There was also no association between MRSS (skin score) and PN in our SSc patients to suggest an underlying compression related pathomechanism. This finding is supported by other studies which observed presence of PN in both affected skin and apparently normal skin

in SSc (Poncelet & Connolly, 2003; Provitera et al., 2007). There was no correlation seen with SSc patients with PN and medications they have received.

Our study is not without limitations. Firstly, only a fraction of our patients had serum vitamin B12 and thyroid levels tested due to logistic reasons. But as far as it was known, none of our SSc patients were vitamin B12 deficient. Secondly, the lack of an objective measurement for small fibers is a drawback in assesing small fiber neuropathy.

Peripheral neuropathy in SSc is not uncommon and patients may suffer from chronic pain which contributes as a non-lethal burden in SSc. The management of peripheral neuropathy is not outlined in the current EULAR recommendation of treatment of SSc (Kowal-Bielecka et al., 2017). It is therefore important to address this under recognised clinical manifestation as the involvement of PNS may have relevant impact on the deterioration of muscle strength and range of motion of the joints. The loss of sensation and position sense also increases the risk of falls and foot ulceration. Future studies with a larger cohort of patients need to be conducted to investigate the pathomechanism as well as effective pharmacological and non-pharmacological treatment options of PN in SSc.

7.0 CONCLUSION

The prevalence of peripheral neuropathy in our Malaysian SSc cohort is similar to other studies. There were no significant associations with disease markers suggesting that polyneuropathy may be due to non-disease conditions. This needs to be addressed by the treating clinician as a potential non lethal burden clinical manifestation in SSc patients. A multicentre study with a larger cohort of SSc patients is needed to evaluate further.

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APPENDIX

1. ASSESSMENT OF PERIPHERAL NEUROPATHY IN SSC PATIENTS

Clinical data sheet

Baseline demographics

Name : _____

Date of Birth : _____

Age : _____

Gender: _____

IC number :_____

RN : _____

Contact Number :_____

Occupation :_____

Smoking :_____

Alcohol :_____

Race : _____

Weight :_____

Height :_____

BMI : _____

Blood pressure _____

Years of symptoms onset :_____

Years of diagnosis :_____

Duration of disease :_____

Aetiology :

	Yes	No	Duration
Diabetes Mellitus	☐	☐	
Hypertension	☐	☐	----------
Ischemic heart disease	☐	☐	----------
Cerebral vascular Disease	☐	☐	----------
Chronic Kidney disease	☐	☐	----------
Others	☐	☐	----------

Current and previous medications

Steroids	
NSAIDS	
PPI	
H2 Blocker	
ACEi/ ARB	
Prokinetic s	
Immunosupressants	
Calcium antagonist	
PDE-5 inhibitor	
Prostacyclin analogue (Iloprost)	
Others	

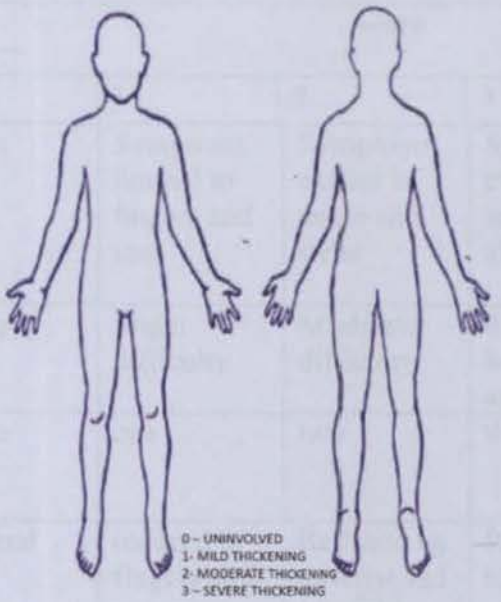
Clinical features

Subset:	Limited	Diffuse	Overlap
Raynaud's			
Digital ulcer or gangrene			
Telangiectasia			
Calcinosis			
Inflammatory arthritis			
Myositis			

Skin

Modified Rodnan Skin Score (total MRSS): **/51**

FACE	0	1	2	3
UPPER ARM	0	1	2	3
FOREARM	0	1	2	3
HAND	0	1	2	3
FINGERS	0	1	2	3
THIGH	0	1	2	3
LEG	0	1	2	3
FOOT	0	1	2	3



FACE	0	1	2	3
UPPER ARM	0	1	2	3
FOREARM	0	1	2	3
HAND	0	1	2	3
FINGERS	0	1	2	3
THIGH	0	1	2	3
LEG	0	1	2	3
FOOT	0	1	2	3

R hand ☐

L hand ☐

GI manifestations

Upper gastrointestinal manifestations ☐

Lower gastrointestinal manifestations ☐

Cardiorespiratory manifestations

Pulmonary fibrosis ☐

PAH ☐

PASP (echo) _____ mmHg EF %

PASP (RHC) _____ mmHg (Normal <25 mmHg)

Dilated cardiomyopathy/myocarditis ☐

Neurological assessment

parameter	score				
	0	1	2	3	4
Sensory symtptoms	none	Symptoms limited to fingers and toes	Symptoms extend to ankle and wrist	Symptoms extend to knee and elbow	Symptoms above knees or elbows or functionally disabling
Motor symptoms	none	Slight difficulty	Moderate difficulty	Requires help or assitance	paralysis
Number of autonomic symptoms	none	one	two	three	Four or five
Pin sensibilty	normal	reduced in fingers and/ or toes	Reduced up to wrist and / or ankle	Reduced up to elbow and / or knee	Reduced above elbow and/ or knees
Strength	normal	Mild weakness	Moderate weakness	Severe weakness	Paralysis
Tendon reflex	normal	Ankle reflex reduced	Ankle reflex absent	Ankle reflex absent, others reduced	All reflex absent

Laboratory investigations

Bloods	Value
Hemoglobin	
Creatinine	
ESR	
CRP	
ANA (pattern)	
ENA	

Nerve Conduction Study

Motor nerve conduction				
Motor nerve NCV(m/s)	segment	Latency (m/s)		Amplitude (mV)
median				
ulnar				
tibial				
Peroneal				

Sensory nerve conduction			
Sensory nerve NCV(m/s)	segment	Amplitude (mV)	
Median sensory			
Ulnar sensory			
Sural nerve			

Informed Consent Form (in English)

Introduction

Peripheral neuropathy in scleroderma has been poorly characterized and the prevalence is unknown. While many patients complain of distal paresthesias, it is unclear whether this represents neuropathic symptoms or cutaneous manifestations of the disease. Our aim is to further evaluate the cause of peripheral neuropathy in systemic sclerosis in our multiethnic Malaysian population

Purpose of study

To assess peripheral neuropathy in scleroderma patients

Type of research intervention

Hospital based cross-sectional study

Sampling method–Consecutive scleroderma patients selected from Rheumatology clinic in UMMC.

Sampling procedure

(1) Patients with inclusion criteria are included in the study after written informed consent is obtained.

(2) Clinical details will be recorded in the proforma/template sheet.

(3) Patients will be questioned on presences of clinical symptoms of neuropathy and neurological examination will be done to assess for evidence of peripheral neuropathy.

(4) Nerve conduction study will be done on each patient, mainly over the upper limbs to asses presence of peripheral neuropathy.

(5) Data analysis will be performed using SPSS 20.0 Statistical Software programme.

Side effects

The 'stimulator' produces small electrical pulses which feel like a sharp tapping sensation. This process is repeated for a number of different nerves. Although some people find it uncomfortable, it cannot do you any harm and there are no side effects.

Potential benefits of the study

To get more information on the prevalance of peripheral neuropathy in scleroderma patient which is not widely recognised and indirectly striving to improve quality of diagnosis and treatment of patients with systemic sclerosis.

The result of the study

Peripheral neuropathy is common among scleroderma patients

Confidentiality

The information obtained from this study will be kept confidential with access only to the researchers.

Sharing the results

Only for research purpose

Further use of sample

There is no further use of the nerve conduction study done.

Right to refuse or withdraw

Participation is voluntary. Patientscan refuse to participate or withdraw from the study anytime. Patients will not lack any benefit from treatment if they choose not to participate in this study.

Whom to contact

If there is any query, during and after the study you can directly contact the investigator Dr. Tharshannia at Rheumatology Unit, University of Malaya Medical Centre (UMMC) or via email: dr.tharsha@gmail.com

Maklumat Untuk Pesakit

Tajuk penyelidikan

Peripheral Neuropathy dikalang pesakit systemic sclerosis

Penyelidik Utama

Dr Tharshannia Balaikerisnan

Dr Raja Jasmin Begum bt. Raja Mohamed

Organisasi

Rheumatology Unit, University of Malaya Medical Centre

Kepada para pesaki yang dihormati

Kami akan menjalankan satu kajian di kalangan pesakit Systemic sclerosis (scleroderma) di klinik SLE dan klinik Rheumatology, PPUM. Anda dijemput untuk menyertai kajian ini.

Pengenalan

Peripheral neuropathy dikalang pesakit systemic sclerosis adalah simptom yang kurang dikenalpasti. Kebanyakkan pesakit systemic sclerosis menghadapi masalah kekebasan tangan dan kaki. Punca utama berasal dari masalah saraf atau manifestasi kulit (fibrosis) masih kurang difahami. Matlamat kami adalah untuk mengkaji simptom kekebasan di kalang pesakit systemic sclerosis and menambah baik sistem peyaring and rawatan di kalangan rakyat Malaysia yang berbagai etnik.

Cara kajian

Penerangan terperinci akan diberikan kepada anda mengenai kajian ini oleh para doktor. Jika anda setuju untuk menyertai kajian ini, anda dikehendaki menandatangani borang persetujuan menyertai kajian. Untuk tujuan kajian ini, berat badan, tinggi dan, tekanan darah akan diukur.

(1) Borang kajiselidik diiisi dan anda akan disoal mengenai penyakit, simptom dan pemeriksaan klinikal akan dijalankan.
(2) Ujian "nerve conduction study" akan dilaksanakan.

Faedah

Untuk mendapatkan lebih banyak maklumat mengenai "peripheral neuropathy" dikalangan pesakit scleroderma. Keputusan daripada kajian ini diharapkan dapat membantu dengan penyaringan dan rawatan peripheral neuropathy pada masa akan datang.

Penyertaan

Penyertaan dalam kajian ini adalah secara sukarela dan anda berhak untuk menarik diri dari kajiian ini pada bila-bila masa tanpa memberi sebab dan tanpa menjejaskan rawatan anda. Identiti anda akan dirahsiakan dan keputusan anda adalah sulit. Anda tidak perlu membuat sebarang bayaran untuk menyertai kajiian ini.

Jika terdapat sebarang pertanyaan, sila hubungi:

Dr Tharshannia
Rheumatology Unit
University of Malaya Medical Centre (UMMC)
Ph : +60167112204

I, ... **Identity Card No**.....

(Name of Patient)

Of .....

(Address)

hereby agree to take part in the clinical research (clinical study/questionnaire study/drug trial) specified below:

Title of Study:Symptomatic and electrodiagnostic features of peripheral neuropathy in systemic sclerosis **the nature and purpose of which has been explained to me by Dr.** .....

(Name & Designation of Doctor)

and interpreted by .....

(Name & Designation of Interpreter)

to the best of his/her ability in ..... **language/dialect.**

I have been told about the nature of the clinical research in terms of methodology, possible adverse effects and complications (as per patient information sheet). After knowing and understanding all the possible advantages and disadvantages of this clinical research, I voluntarily consent of my own free will to participate in the clinical research specified above.

I understand that I can withdraw from this clinical research at any time without assigning any reason whatsoever and in such a situation shall not be denied the benefits of usual treatment by the attending doctors.

Date: ..... **Signature or Thumbprint** .....

(Patient)

IN THE PRESENCE OF

Name .....)

Identity Card No. .....) **Signature**

(*Witness for Signature of Patient)*

Designation .....)

I confirm that I have explained to the patient the nature and purpose of the above-mentioned clinical research.

Date ..... **Signature**.....

(Attending Doctor)

Saya,.....No.Kadpengenalan .....

(Nama Pesakit)

beralamat.....*(Alamat)*

dengan ini bersetuju menyertai dalam penyelidikan klinikal (pengajian klinikal/pengajian soal-selidik/percubaan ubat-ubatan) disebut berikut:

TajukPenyelidikan:Symptomatic and electrodiagnostic features of peripheral neuropathy in systemic sclerosis**yang mana sifat dan tujuannya telah diterangkan kepada saya oleh Dr.....*(Nama & Jawatan Doktor)***

mengikut terjemahan .....*(Nama & Jawatan Penterjemah)*

..... yang telah menterjemahkan kepada saya dengan sepenuh kemampuan dan kebolehannya di dalam Bahasa / loghat.....

Saya telah diberitahu bahawa dasar penyelidikan klinikal dalam keadaan methodologi, risiko dan komplikasi (mengikut kertas maklumat pesakit). Selepas mengetahui dan memahami semua kemungkinan kebaikan dan keburukan penyelidikan klinikal ini, saya merelakan/mengizinkan sendiri menyertai penyelidikan klinikal tersebut di atas.

Saya faham bahawa saya boleh menarik diri dari penyelidikan klinikal ini pada bila-bila masa tanpa memberi sebarang alasan dalam situasi ini dan tidak akan dikecualikan dari kemudahan rawatan dari doktor yang merawat.

Tarikh: ..... Tandatangan/Cap Jari ..... *(Pesakit)*

DI HADAPAN

Nama .....)

No. K/P.....) Tandatangan

(Saksi untuk Tandatangan Pesakit)

Saya sahkan bahawa saya telah menerangkan kepada pesakit sifat dan tujuan penyelidikan klinikal tersebut di atas.

Tarikh: ..... Tandatangan .....

(doktor yang merawat)