"A STUDY ON CLINICO IMMUNO PATHOLOGICAL CORRELATION OF SKIN AND PULMONARY INVOLVEMENT IN SYSTEMIC SCLEROSIS"

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CERTIFICATE

This is to certify that this dissertation entitled "**A STUDY ON CLINICO IMMUNO PATHOLOGICAL CORRELATION BETWEEN SKIN AND PULMONARY MANIFESTAIONS IN SYSTEMIC SCLEROSIS**" presented here is original work done by **Dr.T.AARTHI PRIYA**, DM Post Graduate in the Department of Rheumatology, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai- 600003 in partial fulfillment of the university rules and regulation for the award of D.M. Branch IX- Rheumatology, under my guidance and supervision during the academic period from 2010-2013.

Dr.V.KANAGASABAI, MD.,
Dean,
Madras Medical College and
Rajiv Gandhi Govt. General Hospital,
Chennai – 600 003.

Dr.S.RUKMANGATHARAJAN, MD., DM., FMMC.,
Professor and HOD,
Department of Rheumatology,
Madras Medical College and
Rajiv Gandhi Govt. General Hospital,
Chennai – 600 003.

DECLARATION

I, **Dr.T.AARTHI PRIYA** hereby solemnly declare that this dissertation entitled **"A STUDY ON CLINICOIMMUNO PATHOLOGICAL CORRELATION BETWEEN SKIN AND PULMONARY MANIFESTAIONS IN SYSTEMIC SCLEROSIS"** was done by me in the Department of Rheumatology, Madras Medical College & Rajiv Gandhi Govt. General Hospital, Chennai-3 during July 2011 to February 2013 under the guidance and supervision of Prof.Dr.S.Rukmangatharajan, MD., DM., FMMC., This dissertation is submitted to the Tamil Nadu Dr.M.G.R.Medical University towards the partial fulfillment of requirement for the award of D.M., Degree in Rheumatology.

Signature of the Candidate

Date :
Place :

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INDEX

ABBREVIATIONS

SSc	:	Systemic Sclerosis
DcSSc	:	Diffuse Cutaneous Systemic Sclerosis
LcSSc	:	Limited Cutaneous Systemic Sclerosis
MMP-12	:	Matrix Metalloproteinase-12
MHC	:	Major Histocompatability complex
TCR	:	T Cell Receptor
PTPN	:	Protein Tyrosine Phosphatase
NSIP	:	Non Specific Interstitial Pneumonitis
UIP	:	Usual Interstitial pneumonitis
VCAM	:	Vascular cell adhesion molecule
VEGF	:	Vascular Endothelial growth factor
PDGF	:	Platelet derived growth factor
PAH	:	Pulmonary arterial hypertension
ACA	:	Anti centromere Antibody

AECA	:	Anti endothelial cell antibodies
ANA	:	Anti Nuclear Antibody
MRSS	:	Modified Rodnan skin score
EULAR	:	European League against Rheumatism
ILD	:	Interstitial lung disease
FVC	:	Forced vital capacity
FEV1	:	Forced expiratory volume in 1 sec.
HRCT	:	High resolution computed tomography
PFT	:	Pulmonary function test
GGO	:	Ground glass opacity
BAL	:	Broncho alveolar lavage
PAP	:	Pulmonary arterial pressure
DL co	:	Diffusion capacity of carbon monoxide

APPENDIX – 1

Assessment of disease severity and prognosis in SSc/T.A.Medsger Jr. et al.,

Table II. Revised preliminary SSc severity scale

Organ system	0 (normal)	1 (mild)	2 (moderate)	3 (severe)	4 (endstage)
1. General	**Wt loss < 5%; PCV 37.0%+; Hb 12.3+ Gm/dl**	**Wt loss 5.0-9.9%; PCV 33.0-36.9% Hb 11.0-12.2 Gm/dl**	**Wt loss 10.0-14.9%; PCV 29.0-32.9% Hb 9.7-10.9 Gm/dl**	**Wt loss 15.0-19.9%; PCV 25.0-28.9% Hb 8.3-9.6 Gm/dl**	**Wt loss 20+ %; PCV < 25.0% Hb < 8.3 Gm/dl**
2. Peripheral vascular	**No Raynaud's; Raynaud's not requiring vasodilators**	Raynaud's requiring vasodilators	Digital pitting scars	Digital tip ulcerations	Digital gangrene
3. Skin	TSS 0	TSS 1-14	TSS 15-29	TSS 30-39	TSS 40+
4. Joint/tendon	FTP 0-0.09 cm	FTP 1.0-1.9 cm	FTP 2.0-3.9 cm	FTP 4.0-4.9 cm	FTP 5.0+ cm
5. Muscle	Normal proximal muscle strength	Proximal weakness, mild	Proximal weakness, moderate	Proximal weakness, severe	**Ambulation aids required**
6. GI tract	**Normal esophagram; normal small bowel series**	Distal esophageal hypoperistalsis; small bowel series abnormal	Antibiotics required for bacterial over-growth	Malabsorption syndrome; episodes of pseudo-obstruction	Hyperalimentation required
7. Lung	**DLCO 80+%; FVC 80+%; No fibrosis on radiograph; sPAP < 35 mmHg**	**DLCO 70-79%; FVC 70-79%; basilar rales; Fibrosis on radiograph sPAP 35-49 mmHg**	**DLCO 50-69%; FVC 50-69%; sPAP 50-64 mmHg**	**DLCO < 50%; FVC < 50%; sPAP 65+ mmHg**	**Oxygen required**
8. Heart	**EKG normal; LVEF 50+%**	**EKG conduction defect; LVEF 45-49%**	**EKG arrhythmia; LVEF 40-44%**	**EKG arrhythmia requiring Rx; LVEF 30-40%**	**CHF; LVEF < 30%**
9. Kidney	**No Hx SRC with serum creatinine < 1.3 mg/dl**	**Hx SRC with serum creatinine < 1.5 mg/dl**	**Hx SRC with serum creatinine 1.5-2.4 mg/dl**	**Hx SRC with serum creatinine 2.5-5.0 mg/dl**	**Hx SRC with serum creatinine > 5.0 mg/dl or dialysis required**

Wt: weight; PCV: packed cell volume (hematocrit); Hb:hemoglobin; TSS:total skin thickness score; FTP: fingertip-to-palm distance in flexion; DLCO: diffusing capacity for carbon monoxide, % predicted; FVC: forced vital capacity, % predicted; sPAP:estimated pulmonary artery systolic pressure by Doppler echo; EKG:electrocardiogram; LVEF:left ventricular ejection fraction; Rx:treatment; CHF:congestive heart failure; Hx:history of; SRC:scleroderma renal crisis.

N.B. If two items are included for a severity grade, only one is required for the patient to be scored as having that severity level.

INTRODUCTION

Systemic sclerosis is a chronic autoimmune connective tissue disease of unknown etiology involving multiple systems. It is characterized by significant dysfunction of the microvasculature, immune system and connective tissue.

The currently used classification of Systemic Sclerosis is by the extent of skin involvement[1]. The extent of skin disease correlates with the disease course. Though many internal organs are involved, lung involvement is the major cause of morbidity and mortality in SSc. While some studies regard skin involvement as a surrogate marker for pulmonary involvement, there are studies that have shown improvement of sclerosis occurring spontaneously or as a result of treatment and therefore it does not reflect the pulmonary fibrosis. In addition several cutaneous features have been found to be associated with clinical and serological manifestations in systemic sclerosis. In a recent study[2] elevated serum level of MMP-12 correlated with the severity of skin fibrosis and activity of interstitial lung disease in systemic sclerosis, suggesting the common pathogenesis between them. So the skin can be useful marker for early diagnosis and to assess pulmonary involvement.

AIMS AND OBJECTIVES

- To study the skin and pulmonary manifestations in Systemic Sclerosis.
- To study the correlation of the clinical, pathological, immunological features of skin and pulmonary involvement in Systemic Sclerosis.

REVIEW OF LITERATURE

Systemic Sclerosis(SSc) is a chronic autoimmune disease of unknown etiology. It can affect the skin and other internal organs.

It has a chronic course seen commonly in women and is heterogenous in its clinical manifestations. The hall mark of SSc is the involvement of the skin which becomes thick and indurated (Scleroderma).

Scleroderma spectrum disorders consists of

- Systemic sclerosis.
- Localized scleroderma.
- Infiltrative disorders (Amyloidosis, Scleromyxedema, Scleroderma of Buschke).
- Inflammatory conditions (overlap connective tissue disease, eosinophilic fascitis, chronic graft versus host disease, sarcoidosis).
- Metabolic disorders (myxedema, porphyria, cutaneous tarda, congenital prophyria, acromegaly).

Diffuse and limited cutaneous forms are the 2 major subsets of SSc. Diffuse cutaneous type has progressive course and organ failure occur within 5 years of onset. Whereas in limited cutaneous type , major organ involvement occurs later in the disease course.

PRELIMINARY ACR CLASSIFICATION CRITERIA FOR SYSTEMIC SCLEROSIS

Preliminary ACR classification criteria[3] for Systemic Sclerosis consists of 1 major and 3 minor criteria.

Major criteria

Scleroderma proximal to the metacarpophalangeal joints.

Minor Criteria

1. Sclerodactyly.

2. Digital pitting scars or loss of finger pad substance.

3. Bibasilar pulmonary fibrosis.

Systemic Sclerosis should satisfy 1 major and 2 minor criteria.

Classification based on skin involvement is

1) Diffuse cutaneous SSc: Skin thickening widespread, involving trunk, proximal extremities, distal extremities and and face.

2) Limited Cutaneous SSc: Skin thickening only distal to elbow and knees, face and neck may be involved.

3) CREST Syndrome: Subset of limited cutaneous SSc and consists of calcinosis, Raynauds phenomenon, sclerodactyly, esophageal dysmotility and telangiectasias.

4) Overlap SSc: Features of SSc and its skin changes present along with features of another connective tissue disease like SLE, RA or Myositis.

5) SSc sine sclerosis: Characteristic internal organ involvement, serologic abnormalities and Raynaud's Phenomenon are present without any skin involvement.

EPIDEMIOLOGY

SSc is a sporadic disease and there is variation in the incidence and prevalence in different geographic areas. The study by Mayes et al[4], the incidence ranges from 9 to 19 cases per million/ year and the prevalence rates are 28 to 253 cases/ 1 million/ year in the united states.

GENDER

It is most common in women than men, with female to male ratio ranging from 4:1 to 6:1[5]. Female preponderance may be due to

hormone use or pregnancy, microchimersim or preferred skewing of X chromosome inactivation, towards one parental source. Microchimerism occurs normally during pregnancy due to cell transfer from fetus to mother resulting in genetically distinct small populations[6]. These cells persist through decades and may contribute to the pathogenesis of autoimmune disease.

ETIOLOGY

In SSc, the etiology is unknown.

Genetic factors contribution in SSc is uncertain. Disease concordance in both mono and dizygotic twins are similar. Study by Arnett et al[7] showed the risk of systemic sclerosis with positive family history was 1.6% while in general population were 0.026%. Weak association with DRB1 *11 and DRB1 * 0301 were shown in early studies. Single nucleotide polymorphism in PTPN 22 & IRF5 have been associated with SSc[8]. By European / US GWAS analysis showed there is a role of the MHC, IRF5 and STAT4 gene regions as genetic risk factor for SSC. CD 247 (Locus which codes for TCR subunit), CDH7, IRF4 are additional genetic loci identified by GWAS. There is altered gene expression in the skin of the two subtypes of SSc.

Diffuse cutaneous SSC can be subdivided into 2 groups based on expression of distinct gene clusters which are “Signatures” indicating proliferation or inflammation[9]. The two subgroups are stable overtime, suggesting heterogenecity rather than different stages of same process.

INFECTIOUS AGENTS

Human cytomegalovirus, human parvovirus B19 infection are implicated as potential triggers[10]. Presence of antibodies directed against hCMV derived proteins epitopes UL 83 and UL 94, have been detected in the serum of SSC patients[11]. Anti topoisomerase1 antibody cross reacts with hCMV derived protein, so molecular mimicry may be a mechanism linking hCMV infection and SSc.

ENVIRONMENTAL AGENTS, DRUGS AND RADIATIONS

Toxic oil syndrome, due to ingestion of contaminated rapeseed cooking oils, contaminated L-tryphophan dietary supplements, exposure to certain gadolinium containing radiology imaging dyes produced scleoderma like skin induration with or without multi-system involvemen[12].

Exposure to silica, heavy metals, mercury, organic chemicals like vinyl chlorides, benzene, toluene are implicated in SSc. Cigarette smoking does not appear to have a role in etiology of SSc.

Drugs implicated in SSc like illness are bleomycin, Pentazocine, Cocaine, Fenfluramine etc. Radiation given for malignant neoplasms has been linked with new onset SSc as well as exacerabation of pre-exsiting SSc [13].

PATHOLOGY

The pathologic hallmarks of SSc are a non inflammatory proliferative / obliterative vasculopathy involving small arteries and arterioles in the multiple vascular beds along with interstitial/ vascular fibrosis in the skin, lungs and other internal organs.

Vasculopathy

The primary pathogenetic event in SSc is vascular injury and activation. Histopathologic evidence and clinical signs of vasculopathy occur before fibrosis and other disease manifestation[14].

Initial endothelial injury causes endothelial cell activation and dysfunction. The increase in adhesion molecules, endothelial 1 production result in impaired vasodilation, increased vasoconstriction and lead to endothelial dysfunction. This results in vascular wall remodelling and vascular obliteration finally leading to tissue hypoxia and fibroblast activation.

These is bland intimal proliferation of the small and medium sized arteries and expansion of the intimal layer. Vasculitis or deposition of immune complex on the vessel wall is rare. The clinical signs of vasculopathy are Raynaud's Phenomenon, cutaneous telangiectasia, digital pit formation, nail fold capillary alteration, pulmonary hypertension, scleroderma renal crisis and gastric antral vascular ectasia.

As the disease progresses fibrosis deposition and perivascular fibrosis occur, leading to obliterative vasculopathy and chronic tissue hypoxia[15].

Tissue Fibrosis

Excessive accumulation of type-I collagen along with other fibrillar collagen, fibronectin, elastin, proteoglycans and COMP results in tissue fibrosis. This process disrupts the tissue and organs and contributes to progressive dysfunction and organ failure. The most prominently affected organs are skin, lungs, GIT, heart, perifascicular tissue around the muscle, and tendon sheaths.

ORGAN SPECIFIC PATHOLOGIC FINDIGNS

Skin

Fibrosis of the skin causes marked expansion of dermis and obliteration of sweat glands, hair follicles and other skin

appendages. Collagen fiber accumulation is prominent in the reticular dermis. With progression, the subjacent adipose layer is gradually involved with entrapment of fat cells. In the early stages, there is deep dermal inflammatory cells composed mainly of T lymphocytes, monocytes and less commonly eosinophils and mast cells. The myofibroblast, which are mesenchymal contractile cells are increased and they play a major role in fibrogenesis. As time progress, the skin undergoes atrophy with epidermis thinning and effacement of rete pegs. Decrease in dermal capillaries contribute to tissue hypoxia which can occur even in apparently normal skin of patients with Scleroderma.

Study by Jens T Van Pret et al[16] revealed that the mean epidermal thickness, myofibroblast score and hyalinised collagen score were linked to local clinical skin involvement and correlated well with the local skin score. Myofibroblasts and intima proliferation of the deep arterioles or parakeratosis in skin biopsy are useful specific diagnostic markers for SSc but with low sensitivity.

Biochemical analysis show that the fibrotic dermis have major fibrillar collagens, type I and III collagens similar to the normal skin. But type 7 collagen, minor nonfibrillar collagen,

which is normally restricted to the dermal epidermal basement membrane were present in excess throughout the lesional dermis. Enzymes mediating post translational collagen modification like lysyl hydroxylase (PLOD2) is increased and they contribute to densely sclerotic nature of fibrotic dermis[17].

LUNGS

The earliest change in patients with scleroderma with interstitial lung disease are patchy lymphocytes and plasma cell infiltration of the alveolar walls. In this stage, alveolar lavage fluid contains inflammatory leukocytes and cells of the polarised Th2 immune response. As disease progresses, lung inflammation subsides with interstitial fibrosis and vascular damage will predominate, though both make coexist within the same lesion.

In pulmonary fibrosis local accumulation of collagens and other tissue proteins results in the expansion of the alveolar interstitium. Non Specific Interstitial Pneumonitis (NSIP) is the most common histologic pattern characterised by mild to moderate interstitial inflammation, type 2 pneumocyte by hyperplasia and early uniform distribution of fibrosis. Usual Interstitial Pneumonia (UIP) in less common pattern in SSc -ILD with features of patchy fibrosis and carries a worse prognosis when compared with NSIP

pattern. In 2 studies, NSIP occurred in 78% of 80 patients and 68% of 19 patients respectively[18]. Fibrotic NSIP was seen in most patients, while cellular NSIP occurred in one quarter of the patients within the NSIP pattern. The UIP pattern occurred in 8% and 26% of patients in the 2 studies[19].

PATHOGENESIS OF FIBROSIS

The pathogenesis of SSc is complex and not completely understood. A holistic approach must integrate the 3 cardinal features of SSc (i) Vascular injury and damage (2) activation of the innate and adaptive autoimmunity (3) generalized fibrosis.

Upregulated adhesion molecules VCAM-1 and ICAM-1 in SSc skin along with MHC Class-II provide a cognate endothelial interaction with T Cells..

The study in the UCD 200/ 206 chicken model of scleroderma showed presence of dermal endothelial cell apoptosis in dermal vessels of early SSC patients. But recent study[22], questioned the importance of apoptosis in SSC vasculopathy due to lack of caspase 3 staining.

Upregulation of α2c adrenoreceptors during stress results in exaggerated cold induced vasospasm, Raynaud's Phenomenon. The

resulting ischemic reperfusion injury has profound effects on vascular cells. Hypoxia induces expression of ET-1 (Endothelin-1), VEGF and PDGF, inhibiting eNOS and enhances endothelial cell apoptosis.

Increased plasma ET-1 levels are associated with diffuse cutaneous subset, Pulmonary Arterial Hypertension (PAH), Pulmonary fibrosis and scleroderma renal crisis.

ET-1 plays a important role in the vascular pathology of SSc and is evidenced in the BUILD-2 study[23] by the efficacy of the dual endothelin receptor antagonist bosentan in preventing ischemic digital ulcers and improvement of PAH. There is increased ET-1 and ET-1 receptor expression in the skin and lung tissue of SSc patients as ET-1 enhances type-I and III collagen synthesis, fibroblast proliferation, while decreasing expression of MMP-1.

There is activation of the innate and adaptive arms of the immune system in early SSc with prominent autoimmunity. Activated CD4 and CD8 T lymphocytes, monocytes/ macrophages, eosinophils, mast cells and natural killer cells are seen in perivascular region of the skin, lung and other affected organ. They are detected even before the occurrence of fibrosis.

The skin severity and progression correlates with the extent of lymphocytic tissue infiltrates. There is skewing of immune response toward a Th 2 pattern as Th2 cytokines like IL-4, IL-5, IL-13 are pro fibrotic and stimulates TGFβ, collagen synthesis and myofibroblast transdifferentiation. SSc skin biopsy specimens with clones of CD4 + T cells shows Th2 cytokines profile, similarly alveolar CD8 + T cells from SSc patients shows revealed Th 2 cytokine production. The Th 2 predominance predicts decline in lung function.

CELLULAR DETERMINANTS OF FIBROSIS

Cellular determinants of fibrosis are fibroblast, myofibroblast, pericytes and fibrocytes.

Inappropriate fibroblast activation causing exaggerated ECM accumulation and remodelling is the fundamental pathogenetic mechanism for the fibrosis in SSc.

Myofibroblasts arise from fibroblasts in response to TGF β and express smooth muscle actin, synthesize collagen, MMP inhibitors and ECM components[20]. They are great source of TGF β in the fibrotic response.

Pericytes are mesenchymal cells present normally in the wall of microvessels and maintain vascular homeostasis. In SSc, activated pericytes differentiate into fibroblasts and myofibroblasts thereby linking fibrosis and microvascular injury.

Fibrocytes are CD 34+ mesenchymal cells derived from bone marrow and can synthesize collagen and present antigen.

MOLECULAR DETERMINANTS OF FIBROSIS

Though there are many potent mediators of tissue fibrosis, transforming growth factor β1 (TGF β) has received importance as a very potent profibrotic factor and master regulator of physiologic and pathologic fibrosis. Studies have shown upregulated expression of TGF β1 and TGF β1 ligand in the skin and lungs of SSc patients.

TGF β is secreted by platelets, T-Cells, monocytes/ macrophages as a latent complex which is activated by proteolytic enzymes, integrin and thrombospondin. TGF β binds to the specific surface receptors and trigger intracellular signal transduction leading to induction of target genes[21]. TGF β signalling in fibroblasts is by both the Smad (canonical) pathway and non Smad pathway which involve protein kinases (MAP kinases, JNK, focal adhesion kinase FAK and non receptor tyrosine kinase CAbl).

Egr-1 is a DNA transcription factor induced at sites of acute injury and it increases collagen gene expression and production of TGF β.

Peroxisome proliferator- activated receptors- γ a nuclear steroid hormone receptor and transcription factor in adipogenesis is reduced in SSc, lesional skin biopsies and lung. Thereby suggesting that PPAR-γ has a role in preventing excess fibrosis.

Other key growth factors that have been implicated in the pathogenesis are platelet derived growth factor PDGF, connective tissue growth factor (CTGF), chemokine monocyte chemoattractant proteins MCP-1 and MCP-3. Chemokine expression, PDGF receptor and ligand expression, TNF α expression occur early in the pathogenesis of scleroderma.

AUTO ANTIBOIDES

Autoantibodies can be detected in nearby all patients with SSc but their direct role in the pathogenesis is not well established.

The pathogenetic autoantibodies implicated in tissue damage in SSc are antiendothelial cell antibodies (AECA) antifibroblast, anticollegenase, anti PDGF receptor and antifibrillin 1 antibodies. AECA play an important role in endothelial cell apoptosis, one of the

pathogenic events in SSc. Ahmed et al[24], found AECA patients in both LcSSc and dcSSc subtypes.

Chizzolini et al[25], detected antifibroblast antibodies in 58% of SSc patients with a greater prevalence seen in dcSSc.

The nuclear autoantibodies targeting antitopoisomerase I (also known as Scl-70), centromere proteins (most consistent is CENP-B), RNA polymerase I and III and nucleolar proteins (like U3, fibrillarin) have specific associations with disease subsets and organ manifestations. The nuclear autoantigens become targets by exposing “neoepitope”, which are antigenic structure not previously recognised by the immune system.

Fragmentation of topoisomerase I results in exposure of cryptic epitopes and makes the peptide immunogenic. Other mechanisms of autoantibodies generation in SSc is molecular mimicry after viral infection, chronic B cell hyperreactivity, increased expression of autoantigenic peptides.

Recent data suggested a role of autoantibodies in innate immunity, as evidenced by TLR-7 response in sera of SSc patients containing antitopoisomerase-I.

SCL7O is a 70 KDa autoantigen seen more commonly in diffuse cutaneous SSc but it may occur in limited cutaneous SSc also. It is prevalence is 15-20% in SSc patients.

Antitopoisomerase-I was associated with pulmonary fibrosis, increased mortality in some studies. In one study[26], Scl 70 correlated with the presence of renal vascular damage as measured by Doppler ultrasonography. Recently the EUSTAR compared the frequency of organ manifestations according to presence of antitopoisomerase-I or anti CENP in a cohort of 2000 ANA positive patients[27]. The study confirmed previous associations, in addition there was increased frequency of musculoskeletal complaints, cardiac disturbances and proteinuria among anti topo I positive patients. Titres of topo-I have been linked to MRSS disease activity and presence of flexion contractures. In vitro studies provide a possible pathogenic role of topoisomerase-I by the evidence of topo-I auto antibodies binding to fibroblast cell surfaces.

Anti centromere autoantibodies (ACA) are found in 20-30% of SSc patients and are most commonly associated with LcSSc, calcinosis, ischemic digital loss and pulmonary hypertension[28]. Anti CENPs can be detected by IIF, ELISA and line immunoassay.

Pulmonary fibrosis is negatively associated with ACA. The EUSTAR found ACA linked to increased time lag to overt clinical disease, less musculoskeletal and myocardial involvement and a high risk of intestinal symptoms and hypertension.

Antibodies to polymyositis /Scl autoantigen is seen in 24% of polymyositis/ SSc overlap and 3% of SSc patients. Recent study[29] showed that PM/Scl is cleaved during apoptosis raising the possibility that fragmentation of protein leads to loss of immunogenic tolerance to the autoantigen.

Antifibrillarin (anti U3 ribonucleoprotein) are directed against protein components of small U3, nucleolar RNP complex and are associated with dCSSc, male gender, increased internal organ involvement.

RNA Polymerase I and II autoantibodies are highly specific for SSc and found to be associated with dcSSc, renal crisis and decreased survival[30].

Th/To antibodies are directed against the ribonuclease P complexes and ribonuclease mitochondrial RNA processing subunits. They are seen in 2-5% of SSc patients and are associated

with increased severity of pulmonary fibrosis, decreased survival, milder cutaneous involvement and SSc sine scleroderma[31].

Anti Ku antibodies bind to nucleus and nucleolar proteins of interphase cells and have been detected in 1-14% of patients with SSc.

The small nuclear ribonucleoproteins (SnRNPs), are uridine rich RNA and involved in DNA gene transcuption of mRNA. Study by Asano et al identified U1 RNA antibodies in 61% of SSc patients and observed that these antibodies may be marker for development of pulmonary fibrosis.

Anti histone auto antibodies occur in 16-29% SSc patients and were associated with pulmonary fibrosis, renal and cardiac involvement and increased mortality.

Expression of both antihistone antibodies and ACA were associated with severe pulmonary and vascular disease.

CLINICAL FEATURES

SKIN

Skin involvement is the cardinal feature of SSc, it develop initially in the fingers and hands. The common early cutaneous manifestation is the non pitting edema of fingers, followed by skin

thickening and disabiling sclerosis of the fingers. In limited subset, patients have skin changes confined to face, neck and distal extremities (below the knees and elbows). The skin involvement is usually preceeded by Raynaud's Phenomenon and different patterns can occur at presentation.

In diffuse SSc skin involvement in the hands, forearms, arms, chest, abdomen, thighs, legs and feet is seen.

The changes are more consistent in diffuse SSc with initial edema of soft tissue of hands, legs followed by skin thickening, dermal fibrosis and sclerosis.

As the sclerosis is progressing proximally the advancing edge of the involved skin is identifiable.

Then the skin over the trunk, upper arms and thigh are involved. In early stage of DcSSc proximal skin involvement may be absent and appear like limited cutaneous type with only distal skin thickening. However over 2 years of disease course skin involvement of the trunk and proximal extremities occur.

Thus, it decreases the reliability to classify patient as limited subset within the initial 2 years of onset of skin involvement.

There are 3 phases of skin changes, namely early, established and late.

EARLY PHASE

It is the initial inflammatory and edematous phase presenting as puffiness of hands and feet as the only feature thereby making a diagnosis difficult. This phase may last for 12-18 months.

ESTABLISHED PHASE

The skin becomes firm, taut, hidebound especially proximal to the MCP joints and adherent to deeper structures permitting a definite diagnosis of SSc. It is a longer phase with progressive skin fibrosis. Barnett's sign is the ridging of skin on the neck and is seen both limited and diffuse types. Skin thickening in the face and perioral region produces typical facial features associated with SSc like beak shaped nose, reduced aperture of the mouth (microstomy), radial furr owing around the mouth and finally expressionsless, "mauskopf" (mask like) facies. Fibrosis and atrophy of mandible results in gum and lips retraction causing front teeth to appear prominent.

In this phase, the skin may be coarse, dry and pigmented. There is thinning of epidermis, decreased sweating, hair growth ceases and skin creases disappear.

Skin pigmentation, changes of both hypo and hyper pigmentation occur in the early inflammatory and progressive fibrosis phase. Areas of depigmentation occur over scalp, chest, upper back, pretibial, dorsum of hand and other pressure areas.

These hypopigmented areas give the skin a “salt and pepper” appearance due to the perifollicular sparing of pigment loss.

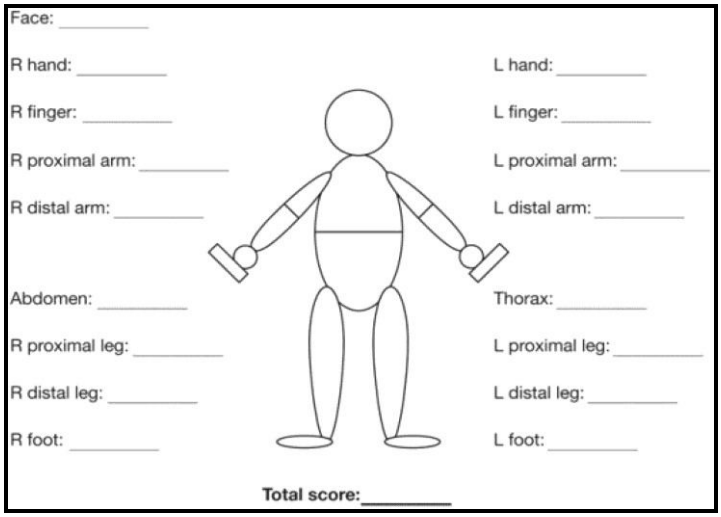
LATE PHASE

After 2 years of disease duration, skin softening occurs. Secondary epithelial structures recover and regrowth of hair in the forearm is an early feature of skin softening. Skin will appear clinically normal over the trunk and upper area.

MODIFIED RODNAN SKIN SCORE(MRSS)

Rodnan pioneered a semiquantitative skin score to measure skin thickness that correlated with skin biopsy specimen weight and reflected the increased collagen content[32]. The original score had 26 areas, 0-4 grading with range of 0-104. This score was subsequently simplified as modified Rodnan skin thickness score (MRSS). Skin thickness is assessed by palpation of 17 areas (Figure) and rated by scores from 0 to 3 in each areas with range 0-51.

Modified Rodnan Skin Score: 17 Sites to be assessed



0- Normal skin.

1- Mild skin thickening.

2- Definite (established) thickening without fixation to deeper tissues.

3- Hide bound skin/ severe thickening with fixation to deep tissues.

Study by Furst DE et al, found MRSS as an accurate reflection of skin biopsy thickness in systemic sclerosis with good reliability and sensitivity to changes[33].

Using skin score data of patients, Steen and Medsger et al found MRSS, provided a surrogate measure of disease severity and had prognostic value, especially in dcSSc[34]. Patients with highest

peak skin score were least likely to improve and experienced significantly severe organ involvement.

In early diffuse systemic sclerosis trial[35] reported that a high baseline MRSS was associated with baseline cardiac involvement and predicted increased mortality and scleroderma renal crisis.

The skin score greater or equal to 15 at the entry was associated with greater risk of early fatal renal and cardiac complications.

In a prospective study of Ketanserin Vs placebo in SSc they found a strong correlation between MRSS and dry and wet weights of forearm skin biopsy. In this study the wet weight was higher in the DcSSc biopsy, thereby supporting the usefulness of MRSS to differentiate the SSc subtypes.

A recent clinicopathological study[37] showed MRSS correlated with histological extent of skin fibrosis as well as the TGF β signalling in SSc fibroblasts (as measured by the increased smad3 phosphorlyation levels). Thus MRSS is well validated and reflects the underlying pathogenesis of SSc.

Novel tools to assess the skin involvement are durometer, high frequency ultrasound, vestometer and elastometry.

Durometer are hand held device that can be used to objectively measure skin thickening and hardening. Merkel et al[38] demonstrated that the durometer measurements are reliable, valid and showed better sensitivity compared to MRSS. In the recent study[39] durometer scores correlated well with MRSS scores of fingers, hands, forearm, upper arm, thighs and feet, but poorly correlated with MRSS at the chest, abdomen and lower legs.

A recent novel portable device, the electronic tonometer, to assess the skin hardness by measuring deformation produced by a known weight or force was used by M.Dugar et al[40]. They found skin hardness assessed by the device correlated well with the total MRSS, in addition it was able to detect minor changes. Other cutaneous manifestations are digital ulcers, digital pitted scars, cutaneous telangiectasia and calcinosis.

DIGITAL ULCER

Digital ulcers is a significant clinical problem seen in 40-50% of SSc patients[41]. Significant vasopasm, digital vasculopathy, dermal fibrosis, epidermal atrophy and local trauma are risk factors

for digital ulceration in SSc[42]. Digital ulcers occur at fingertips, finger creases, and less commonly on the toes, causing pain and functional impairment. Chronic ulcers have 15% complication rate, which include infection, gangrene, osteomyelitis and amputation. One amputation increase the chance of further amputations by 1-2% in the next 6-12 months.

In a study to detect possible risk factors in SSc patients with digital ulcers, possible association between digital ulcers with PAH was postulated[43]. The digital ulcer and PAH have similar vasculopathy changes of fibrotic intimal hyperplasia, adventitial fibrosis and decreased arterial lumen. Studies using German Network for SSc and French Itiner AIR sclerodermic registry had identified association of digital ulcers with male sex, Scl 70 antibodies[44] and early age at onset[45].

Digitals ulcers were found to have negative impact on the physical and mental components of quality of life[46].

Digital ulcers can be active and healed ulcers. In active ulcers, there is denuded areas with defined border loss of epithelialization epidermis and dermis loss. Healed ulcers are characterized by complete epithelialization of the ischemic ulcer.

DIGITAL PITTING SCARS

Digital pits is a part of ACR criteria for SSc and represent areas of ischemic insult. It need not be preceded by digital ulcers.

They appear as pinhole sized depression with hyperkeratosis.

Digital pitted scars were seen in 39% of SSc patients and was found to associated with Raynaud's Phenomenon, skin thickening and joint disease[47].

Disease duration were not associated with the numbers of scars.

Raynaud's Phenomenon occurs in more than 95% of SSc patient. In primary Raynaud's Phenomenon digital vasopasm is reversible without progression to tissue injury. While in SSc patients with Raynaud's Phenomenon progress to digital ischemia resulting in digital ulcers, digital pitted scars and even gangrene. Herrick et al showed that the digital ischemia in SSc is due to abnormalities in neuroendocrine mechanism, vasculature structure (both microvessels and digital arteries), intra vascular factors and oxidative stress[48].

In systemic sclerosis, there is exaggerated generalized vasospastic tendency clinically presenting as Raynaud's Phenomenon as shown by early digital arterial closure after cold

stimulation and inadequate vasodilatory response to heat. It is not only seen in the extremities, but can occur in internal organs[49].

It may be the initial event in the pathophysiology of SSc. Clinically it is characterized by typical tricolour changes primarily in the acral body parts. There is sudden pallor of digits of fingers (white ischemia) followed by reactive erythema (red hyperemia) after rewarming. In severe attacks ischemia followed by cyanosis prior to hyperemia and is associated with pain or dysesthesia.

Vascular changes in systemic sclerosis may at least partially reflect vascular alterations in other organs suggesting a general pathomechanism in SSc[50].

Raynaud's Phenomenon were considered to be associated with a vascular form of pulmonary involvement and PHT. In study by Mukerjee et al, pulmonary vasospasm response to peripheral and central cold challenge did not contribute to persistence of PAH on SSc patients.

Structural vascular abnormalities occur in microcirculation and digital arteries in SSc patients. In the microvasculature, there is decrease in the number of capillaries, abnormal capillaries often with dilated loops, hemorrhages and capillary drop outs.

RP together with abnormal nail fold capillaries are sufficient to diagnosis early SSc[51].

Recently EULAR European League against Rheumatism Scleroderma Trial and Research Group[52] proposed another set of criteria (Yet to be validated) for very early diagnosis of SSc in which there is central role for nailfold capillaroscopy in identifying early SSc.

A study showed that reduced nailfold capillary density in SSc patients associated with established PAH, due to possible pathogenic significance and thus help in detection of this subset at an early stage.

A recent study showed that there was strong association between higher capillaroscopic avascular scores and ground glass lung opacities, especially in SSc patient with <5 years disease duration[53].

Recent large study[54] showed SSc patients with PAH had lower capillary density when compared with SSc patients without PAH, but loop dimensions were equal in both. The reduction in nailfold capillary density correlated with severity of PAH in SSc and idiopathic PAH.

Widefiled microscopy is entirely non invasive method in which nailfold capillaries running parallel to epidermis can be examined under a light microscope with magnification of x12 x14[55].

Nailfold video capillaroscopy(NVC) is an extension of the original widefield technique,with a videocamera connected to the microscope with higher magnification.

Cutola et al[56] reclassified microvascular alteration into 3 defined NVC patterns (early, active, late).

There is association between capillary pattern and disease subtype and autoantibody status.

PULMONARY MANIFESTATIONS

Pulmonary disease is an important component of SSc with an estimate of 80% of SSc patients showing evidence of pulmonary involvement.

It is the leading cause of death in SSc patients contributing 33% to the mortality[57]. The common pulmonary manifestations of SSc are interstitial lung fibrosis and pulmonary hypertension while other pulmonary manifestations include pleural effusion, aspiration pneumonia, bronchiectasis, endobronchial telangiectasia with

hemoptysis, obstructive airway disease cryptogenic organizing pneumonia and lung neoplasms.

Lung fibrosis occurs in both limited and diffuse cutaneous scleroderma, but is more commonly in diffuse subset. Though only 40% of SSc patient have clinically evident ILD, autopsy findings reveal higher percentage of 80% prevalence, range from 25% to 90% depending on the method used to identify pulmonary fibrosis. Pulmonary function tests defining restrictive lung disease by forced vital capacity <80% predicted value and FEV1 (forced expiratory volume in 1 second) identified 25% of ILD in a study with Danish patients[58].

On using higher resolution computed tomography (HRCT) prevalence of pulmonary fibrosis in patients with scleroderma was as high as 90% in 2 studies.

PREVALENCE IN THE SUBSETS

Using PFT restrictive pattern as marker of pulmonary fibrosis 23% of limited subset and 40% of diffuse subtype had pulmonary fibrosis.

By CXR, 33% of limited SSc and 40% of diffuse scleroderma had pulmonary fibrosis[59].

Sken et al showed that the patients of diffuse SSc and CREST had similar PFT abnormalities[60].

In most patients, onset of pulmonary fibrosis occur within first 3 years of disease onset. After the occurrence of pulmonary fibrosis, greatest loss of lung volume occur within first two years[61].

Clinically symptoms of disease usually occurs in 55% of patients with ILD, whereas cough is dry, non productive and seen less commonly. Rarely hemoptysis can occur, but it may be complication of carcinoma or bronchial talengiectasia. Fine end inspiratory crackles of “velcro” character are heard at lung bases, while pleural rub is very rare.

Esophageal reflux and dilatation was associated with pulmonary fibrosis. In a study, scleroderma patients with severe oesophageal motor dysfunctions on comparison with those with moderate or no oesophageal motor dysfunction, exhibited a higher prevalence of pulmonary fibrosis[62].

Progressive lung fibrosis proceeding to severe restrictive lung disease occurs only in a minority. The risk factors for the progressive nature include ethnic background (Black & Japanese races), diffuse cutaneous scleroderma and anti SCl70 positivity.

Patients with normal PFT at presentation time and stable lung function at follow up period are unlikely to go for severe pulmonary fibrosis,. Patient with low FVC and DLco values at baseline are likely to progress to end stage lung disease.

Decline in DLco have been associated with male sex, severe Raynaud's Phenomenon and PHT.

Anti topoisomerase-I (Anti SCl70) antibodies are associated with increased prevalence of pulmonary fibrosis in all patients, especially in diffuse type. The presence of DR3/ DRW52a anti SCl70 has a relative risk of 16.7 for occurrence of pulmonary fibrosis in scleroderma patients[63]. Anticentromere antibodies have a negative association with prevalence of pulmonary fibrosis.

Chest radiography abnormality occurs in 25%-67% of SSc-ILD patients. The typical reticular pattern in lung bases and periphery is seen in early disease. In advanced disease, there is loss of lung volume, more extensive reticular shadowing and honey combing.

PULMONARY FUNCTION TESTING

PFT is important for the evaluation of dyspnea and detection of pulmonary involvement in SSc patients. Patients with ILD

demonstrate restriction pattern, although in mild disease it may be normal. Total lung capacity by plethysmography is reliable method to confirm lung restriction, but it is a complex procedure. Spirometry is a simple test and measures static lung volumes at rest (vital capacity, forced vital capacity) and dynamic volumes (forced expiratory volume in 1 sec) in flow volume- loops.

In restrictive lung disease, the FVC will be reduced and the ratio of FEV1/ FVC is normal.

In scleroderma patients FVC of less than 75% predicted value is seen in 40% patients indicating presence of ILD.

The diffusing capacity of carbon monoxide (DLco) measures the gas transfer between the inhaled air in the alveoli to the red blood cells in the circulation. Decreased DLco value is seen in 70% of SSc patients, making it the earliest signal of lung disease. It correlates with the extent of disease by HRCT scan. It will be reduced both in ILD and PHT, to differentiate the cause, ratio of FVC/DLco is calculated. If the ratio of FVC/DLco is <1.4, it is parenchymal cause and ratio of >1.4 it is pulmonary vascular involvement. When both ILD and vascular involvement occurs, FVC % and DLco% both are reduced.

The methods used for measuring DLco are single breath method, steady state method and multiple inert gas technique. High resolution computed tomography are sensitive in detecting early pulmonary interstitial fibrosis and accurate in assessing the severity of lung involvement.

The earliest change occur at the juxtrapleural, posterior and basilar portion of the lungs.

The HRCT findings in scleroderma patients are ground glass opacities (defined as increased lung attenuation without architectural distortion), reticular linear opacities (architectural distortion with reticular intralobular interstitial thickening), traction bronchiectasis, subpleural and diffuse honeycombing, small nodules and parenchymal bands[64].

The most common HRCT pattern in SSc-ILD is predominantly ground glass opacity and pulmonary fibrosis consistent of NSIP pattern.

Whereas honeycomb cystic changes, a marker of UIP (Usual Interstitial Pneumonia) is reported in 11% to 37% SSc-ILD patients[65]. Overlap (mixture) of UIP and NSIP patterns may occur in SSc-ILD.

There are criteria for scoring the extent and severity of ILD on the CT scans based on the relative proportion of GGO, reticulations and fibroisis by visual or computer based quantification method. In the visual scoring system[66], lung is divided into three zones (Apex of lung to aortic arch, aortic arch to inferior pulmonary vein and inferior pulmonary veins to lung bases) and in each zone the extent of abnormality is scored on a scale of 0-4 (0-Absent, 1- 1:% to 25%, 2-26% to 50%, 3-51% to 75%, 4: 76%-100%).

Recently simplified scoring system is suggested based on whether less or more than 25% of the lung is affected[67].

The fibrosis on HRCT scans in SSc-ILD patients has been used to predict the progression of fibrosis and response to the treatment. In a study SSc patients with more extensive disease involvement by HRCT (more than 20% of lung volume) had higher mortality and rapid decline in the lung function.

In one study[68], the extent of 4 HRCT patterns of ILD (GGO, reticular, homey comb and mixed) in each lobe were scored. In the HRCT scores, the inflammatory index (GGO and mixed scores) and

fibrosis index (reticular and honey comb scores) were found to correlate with abnormal lung function.

BRONCHOALVEOLAR LAVAGE (BAL)

It is a procedure in which physiological solution (normal saline, plasmalyte or normosol) is instilled into a specified area of lung parenchyma and the fluid is aspirated. The aspirate represents sampling of about 1% of all alveoli. Usually BAL cellularity having more than 3% to 5% neutrophils or >3% eosinophils of the total cell count is considered lung inflammation.

Early studies showed granulocytosis on BAL has been associated with active alveolitis and increased risk of deterioration[69].

But recent studies have shown that elevated neutrophil count in BAL reflect the increased extent of disease involvement on CT, rather than the progression of the disease.

In the scleroderma lung study, the data suggested that BAL granulocytosis did not give any additional prognostic information than the HRCT and PFT values and it was not a predictor of treatment response[70].

The role of BAL in ruling out infection is still important.

The histological subtypes by lung biopsy were similar to radiographic appearance in SSc-ILD. NSIP is the most common pattern seen in 76% of the cases in one study, while UIP seen in 11% of the cases[71]. Rarely organizing pneumonia and diffuse alveolar damage occur. The survival rate did not differ between cellular NSIP, fibrotic NSIP and UIP pattern in a series of 80 patients, indicating that histology has no prognostic value.

PULMONARY HYPERTENSION

Pulmonary arterial hypertension (PAH) is a devastating vascular complication in systemic sclerosis. Inspite of advances in early diagnosis and newer treatment, SSc- related PAH is a leading cause of mortality[72]. The mean pulmonary arterial pressure of more than 25mm Hg with a pulmonary capillary wedge pressure <15mmHg by right sided heart catheterization is a definite diagnosis of pulmonary hypertension[73].

It is mainly due to an occulusive vasculopathy of the pulmonary arterial system leading to increased resistance to pulmonary blood flow with elevated pulmonary pressures. The prevalence of SSc-PAH is 7.8 to 12% in prospective studies, while French registry accounted for 15.3%.

Clinical markers for the increased risk of developing PAH in SSc are limited cutaneous type, disease duration greater than 3 years,the age of onset of SSc, severity or duration of Raynaud Phenomenon, reduced nailfold capillary density and prominent telangiectasia[74]. Serological markers like ACA and antifibrallin antibodies, increase risk of SSc associated PAH.

Isolated reduction of DLco or progressive decrease of DLco is emphasized as an independent predictor of PAH, especially in SSc-PAH.

The gold standard for determining PAH in SSc patients is right heart catheterization enabling to quantify the response of pulmonary vessels to vasodialators and guide in the treatment.

However Doppler echocardiography is useful as an effective and non invasive method to assess the presence and severity of PAH and exclude myocardial or valvular abnormalities.

Doppler echocardiography can be provide a better indication of PAH presence, if the peak velocity of tricuspid regurgitation is assessed. The maximum velocity of the regurgitation jet of the tricuspid valve into the right atrium during ventricular systole is an estimate of right ventricular systolic pressure. The contribution of

elevated echocardiographic systolic PAP along with an elevated right ventricular Tei-index is more reliable indication of PAH[75].

The applications of either of the two approaches will minimize the negative cardiac catheterization.

All SSc patients should be annually screened for the presence of PAH by Doppler echocardiogram .Studies shows that the 8% of SSc patients had PAH at 5 years from the onset of disease and 12% may ultimately be affected in the later disease.

The limitation of Doppler echocardiograph is the rate of false positive or false negative is nearly 30% in the important range of 30 to 50 mmHg of pulmonary artery pressure.

The 6 minute walk test is non invasive method used for assessing the dyspnea severity in CTD related PAH. It is recommended as baseline assessment and to monitor response to therapy in idiopathic PAH and not indepently validated in SSc-PAH[76]. In metaanalysis of involving treatment with bosentan and sildenafil in IPAH and SSc-PAH, there was significant improvement in 6MWD in IPAH and not in SSc PAH patients. In 6MWT requires a integrated response of system needed for daily functioning, so comorbidities like pain and musculoskeletal dysfunction reduce the reliability and validating of this test in SSc patients[77].

MATERIALS AND METHODS

SUBJECTS

Patients attending the Rheumatology Care Centre (RCC) outpatient and inpatient of Rajiv Gandhi Government General Hospital, Chennai were recruited from the period of June 2011 to February 2013. 55 eligible cases who fulfilled the inclusion criteria were enrolled. All subjects gave a written informed consent to enroll in this study. The Ethical committee approval was obtained.

INCLUSION CRITERIA

American College of Rheumatology preliminary classification criteria.

Major criteria or two minor criteria for diagnosis.

Major criteria

Scleroderma proximal to the metacarpophalangeal joints.

Minor Criteria

1. Sclerodactyly.

2. Digital pitting scars or loss of finger pad substance.

3. Bibasilar pulmonary fibrosis.

EXCLUSION CRITERIA

Overlap syndrome, mixed connective tissue disease, other scleroderma spectrum disorders.

CLINICAL AND LABORATORY ASSESSMENT

Detailed history, physical examination and evaluation were done in all patients. Laboratory evaluations including complete hemogram, liver function tests, renal function tests, blood sugar and lipid profile were done. Immunological assays consisting of CRP (Latex agglutination methods), ANA (ELSIA/ Hep2) and ENA profile were done.

Other investigations like ECG, Chest X-ray, USG abdomen was done. HRCT chest using Siemens 4 slice CT scanner with 1mm cut was taken for all the patients.

The extent and severity of skin tightening was recorded with modified Rodnan skin scoring.

PULMONARY FUNCTION TESTS

All cases were subjected to spirometry. The patient are asked to blow maximum after deep inhalation and restrictive pattern was interpreted if the ratio FEV1/ FVC was normal (>70%) with reduced FVC <80% (forced vital capacity) using peak expiratory flow meter.

Diffusion capacity for carbon monoxide (DLco) was done by single breath method. The test gas is a composition of mixture (0.3% Co, 0.3% methane and 21% oxygen). The patient inspires the test gas deeply in less than 4 seconds and after holding the breath for 10 seconds he exhales to the maximum within 4 seconds. Value of <80% is considered decreased. 46 patients underwent DLco.

Medsger's severity scale (appendix-1) which is a disease severity scale for 9 organ system with a score of 0 to 4 applied for skin and lung. (0-Normal, 1-Mild, 2-Moderate, 3- Severe and 4-end stage). This scale was used for the skin and lung to measure the severity and damage.

Skin Biopsy

Under local anaesthesia, incisional skin biopsy from the sclerotic lesion was done for the study cases.

Bronchoalveolar Lavage

In this procedure 100ml of normal saline was instilled through bronchoscope and 2/3rd of the fluid was aspirated back by slow suction and sent for analysis.It was done for 26 cases.

ECHOCARDIOGRAM

2D Echocardiogram was done for all the study cases and pulmonary hypertension was detected by the presence of tricuspid

regurgitant peak gradient (TRPG) of >25 mmHg and graded as mild (<40mmHg), moderate (40-60mmHg) and severe (>60mmHg).

STATISTICAL ANALYSIS

The statistical analysis was performed using the SPSS (Version 11.5). Frequencies are expressed as percentages and other results as mean and standard deviation (SD).

Paired ‘t’ test, one way anova test and Pearson chisquare test was used in this study. P value less than 0.05 was considered statistically significant.

RESULTS

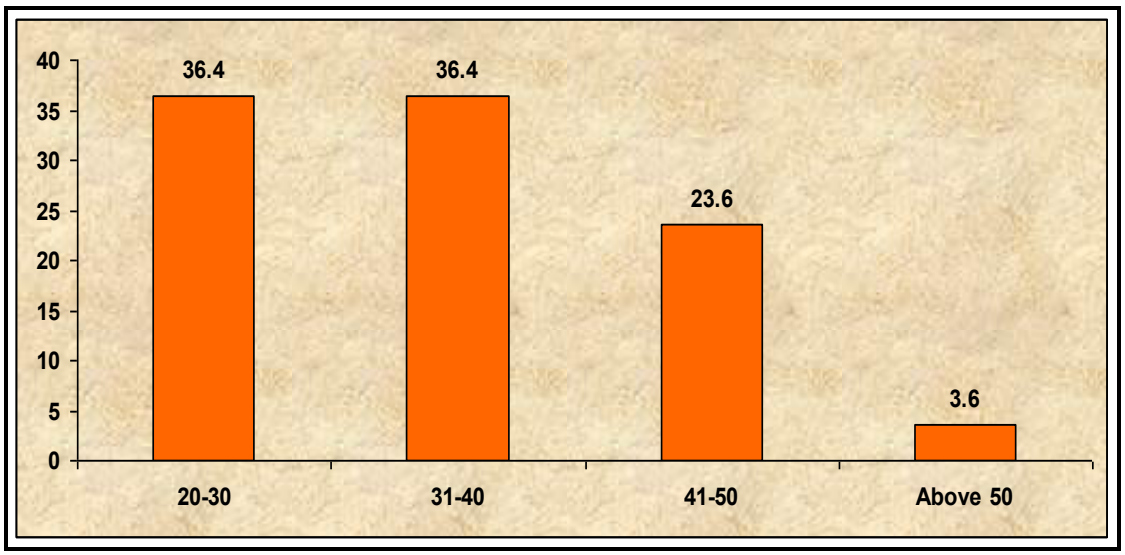
Total number of cases were 55.

The mean age was 35.5 years. The range was from 20-56 years.

Table-1: Age Distribution

Age in years	Frequency	Percent
20-30	20	36.4
31-40	20	36.4
41-50	13	23.6
Above 50	2	3.6
Total	**55**	**100.0**

Figure -1: Age Distribution

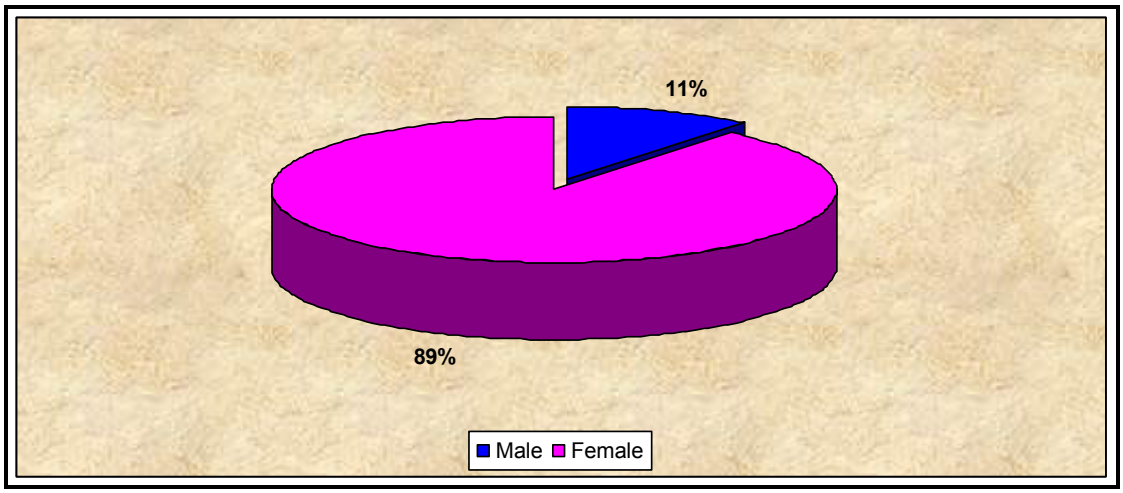


Majority were females 49 (89.1%) while males were 6 (10.9%).

Table-2: Sex Distribution

Gender	Frequency	Percent
Male	6	10.9
Female	49	89.1
Total	**55**	**100.0**

Figure-2: Sex Distribution



The mean disease duration was 3.1 years with range 4 months to 10 years.

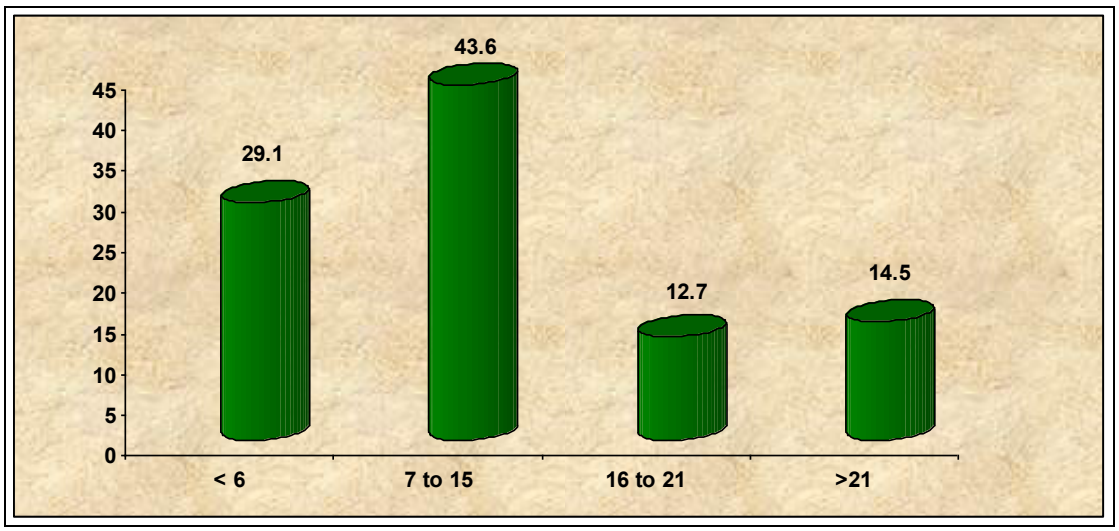
CLINICAL CHARACTERISTICS OF CASES

Limited cutaneous disease was observed in 32 (58.2%) and diffuse cutaneous disease subsets were 23 (41.8%). The MRSS ranges was 4-30 and the mean MRSS was 11.87. Out of 55 patients 16 (29.1%) revealed MRSS <6 and 24 (43.6%) had MRSS 7-15. In the MRSS range of 16-21 and >21, there was 7 (12.7%) and 8 (14.5%) patients respectively.

Table-3: Distribution of MRSS

MRSS	Frequency	Percent
< 6	16	29.1
7-15	24	43.6
16-21	7	12.7
>21	8	14.5
Total	**55**	**100.0**

Figure-3: Distribution of MRSS



Salt and pepper was noted in 38 (69.1%) Digital ulcers was observed in 13 (23.6%). Digital pitted scars were seen in 32(58.2%). Gangrene of digits was observed in 8 (14.5%). Raynaud's Phenomenon was seen in 47 (85.5%) cases.

Table-4: HRCT Lung

HRCT Lung	Frequency	Percent
No ILD	18	32.7
ILD NSIP	25	45.5
ILD UIP	9	16.4
ILD both	3	5.5
Total	**55**	**100.0**

Pulmonary involvement was noted in39 (70.9%). By HRCT Chest, ILD was seen in 37 cases (67.3%).

In the patients with ILD, NSIP pattern was seen in 25 (45.5%), UIP pattern seen in 9 (16.4%) and both pattern together in 3 (5.5%). Pneumonitis was seen in 1 (1.8%) case.

Table-5: Pulmonary Hypertension by ECHO

Pulmonary Hypertension	Frequency	Percent
Absent	47	85.4
Mild	2	3.6
Moderate	3	5.5
Severe	3	5.5
Total	**55**	**100.0**

Pulmonary Hypertension was seen in 8 (14.5%). Both PHT and ILD was seen in 7 (87.5%) cases while isolated PHT seen in 1 (12.5%) cases.

Dyspnea was seen in 39 (70.9%) patients.

Decreased pulmonary function by PFT was seen in 42(76.4%) cases. Restrictive pattern was seen in 34 (61%) cases.

Decreased DLco seen in 28(63%) of 46cases.

Evidence of ILD by Chest X-Ray was seen in 24 (43.6%) cases.

ANA was positive in 44 (80%) cases.

SCL 70 was positive only in 4 (18%) of 23cases.

Skin biopsy evidence of early changes were seen in 9(16.4%) cases and late fibrotic changes seen in 46 (83.6%) cases.

Abnormal BAL changes were seen in 9(24.3%) cases of 37 patients.

ECG changes (non specific ST changes, T inversion) seen in 12 cases.

Table-6: Medsger disease severity scale for lung

Medsger disease severity	Frequency	Percent
Normal	15	27.3
Mild	23	41.8
Moderate	15	27.3
Severe	2	3.6
Total	**55**	**100.0**

Table-7: Relation of the skin and pulmonary variables to MRSS and the percentage of the variables in the different MRSS frequency

Variables	**MRSS**				**Total**	**P Value**
	<6	**7-15**	**16-21**	**>21**		
Mean Disease Duration	16	24	7	8	55	P=0.821
Subtypes						
LC	16(50%)	16(50%)	0	0	32	P=0.000**
DC	0	8(34.8%)	7(30.4%)	8(34.8%)	23	
Salt & Pepper						
Present	5 (13.2%)	18 (47.4%)	7 (18.4%)	8 (21.1%)	38	P=0.000**
Absent	11 (64.7%)	6 (35.3%)	0 (0%)	0 (0%)	17	
Digital Ulcer						
Present	5 (38.5%)	5 (38.5%)	23 (15.4%)	1 (7.7%)	34	P=0.400
Absent	11 (26.2%)	19 (45.2%)	5 (11.9%)	7 (16.7%)	42	
Digital Pitted Scars						
Present	8 (25.0%)	12 (37.5%)	5 (15.6%)	7 (21.5%)	32	P=0.059
Absent	8 (34.8%)	12 (52.2%)	2 (8.7%)	1 (4.3%)	23	
Gangrene						
Present	4 (50.0%)	1 (12.5%)	2 (25.0%)	1 (12.5%)	8	P=0.202
Absent	12 (25.5%)	23 (48.9%)	5 (10.6%)	7 (14.9%)	47	

MRSS was significantly associated with the sub types of limited and diffuse SSc and presence of salt and pepper. No association seen between the disease duration, digital ulcers, digital pitted scars and gangrene with MRSS.

Figure-4: Relation of the SSc Subtypes to MRSS and the percentage of the variables in the different MRSS frequency

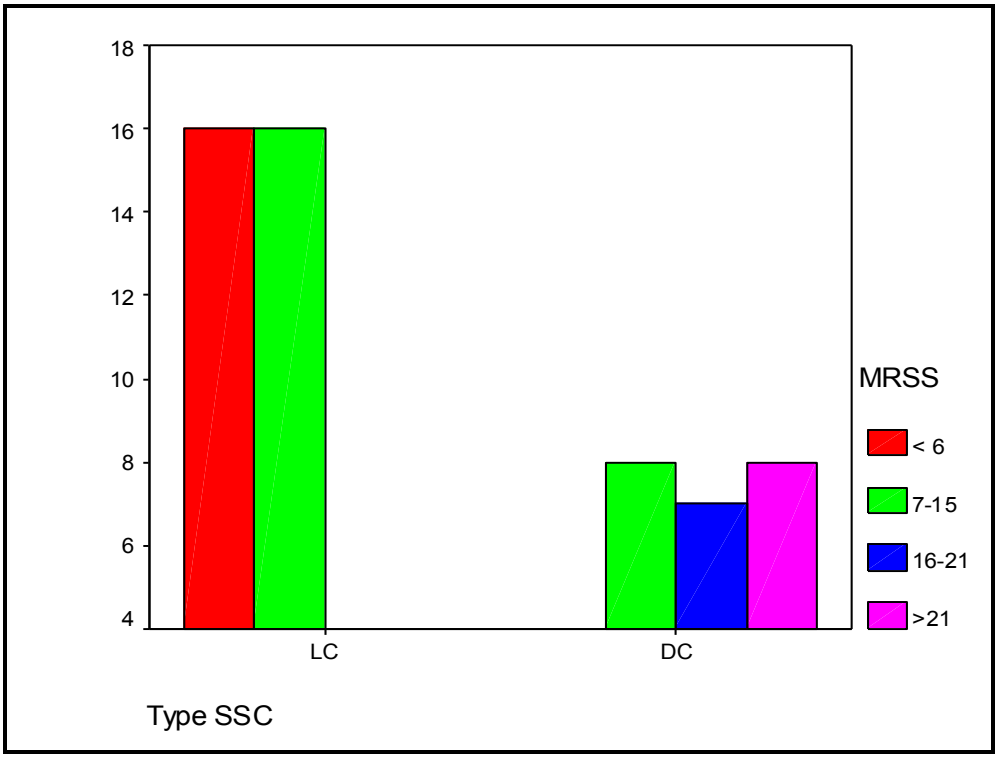


Figure-5: Relation of the Salt and pepper presence to MRSS and the percentage of the variable in the different MRSS frequency

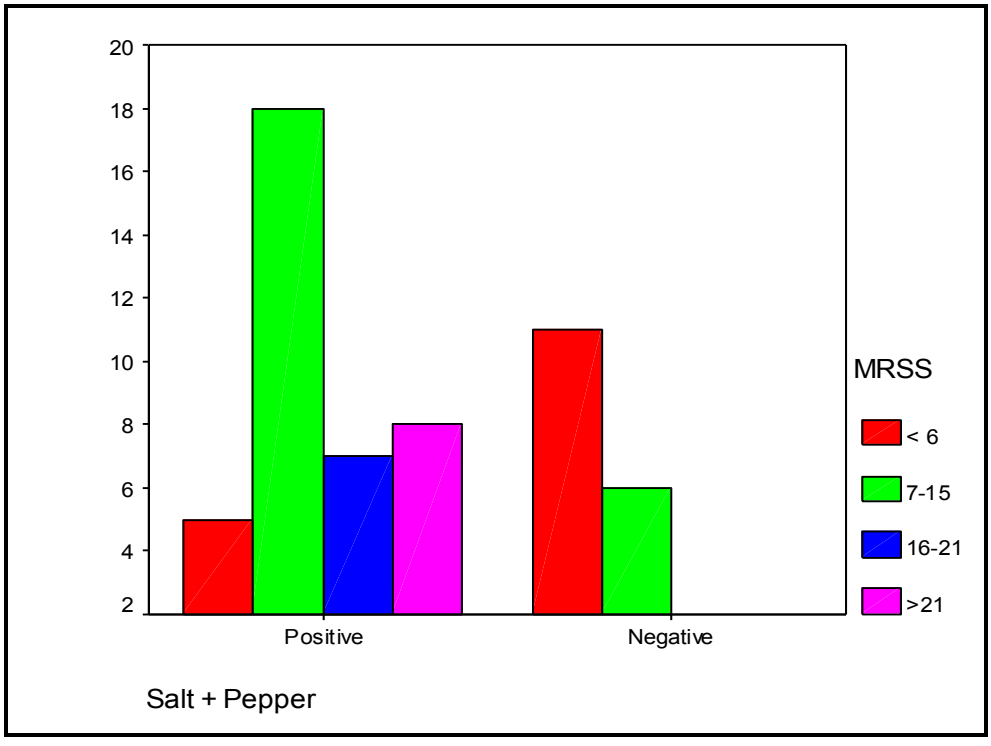


Table-8: Relation of the pulmonary variables to MRSS and the percentage of the variables in the different MRSS frequency

Variables	MRSS				Total	P Value
	<6	7-15	16-21	>21		
Dyspnea						
Present	10 (25.6%)	15 (38.5%)	6 (15.4%)	8 (20.5%)	39	P=0.015*
Absent	6(37.5%)	9(56.3%)	1(6.3%)	0(0%)	16	
Pulmonary Hypertension						
Present	3 (38.5%)	3 (38.5%)	1 (12.5%)	1 (12.5%)	8	P=0.374
Absent	13 (28.3%)	21 (48.7%)	6 (11.9%)	7 (15.2%)	47	
ILD by HRCT						
Present	10 (27.0%)	15 (40.5%)	6 (16.2%)	6 (16.2%)	37	P=0.050*
Absent	6 (33.3%)	9 (50.0%)	1 (5.6%)	2 (11.1%)	18	
PFT						
Reduced	10 (27.0%)	18 (42.9%)	7 (16.7%)	7 (16.7%)	42	P=0.217
Normal	6 (46.2%)	6 (46.2%)	0 (0%)	1 (7.7%)	13	
Disease Severity of Lung						
Present	10(25%)	16(40%)	7(17.5%)	7(17.5%)	40	P=0.025*
Absent	6 (40.0%)	8 (53.3%)	0 (0%)	1 (3.0%)	15	

MRSS was significantly associated with dyspnea, ILD and Medsger disease severity score of lung. No association seen between pulmonary hypertension, reduced PFT with MRSS.

Figure-6: Relation of ILD to MRSS and the percentage of the variables in the different MRSS frequency

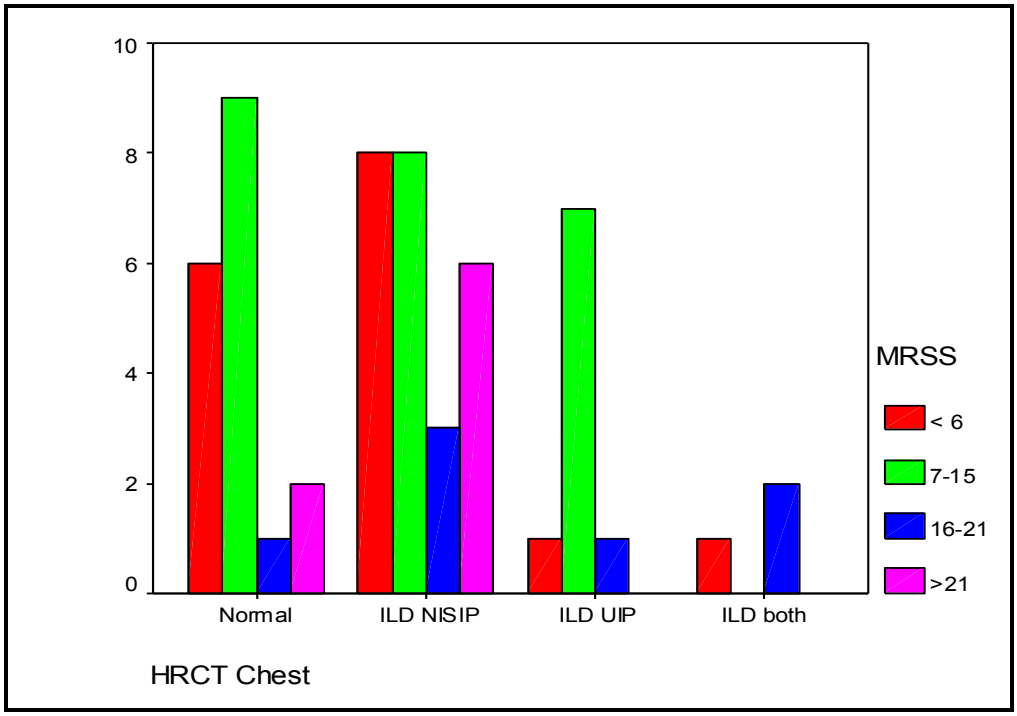
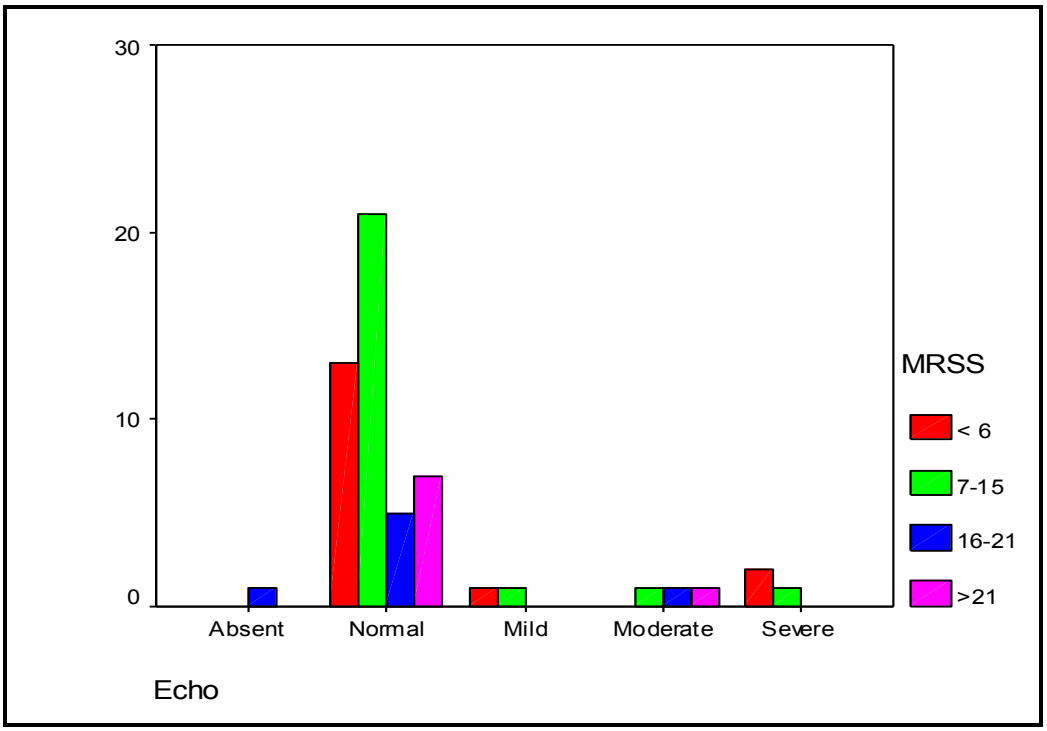


Figure-7: Relation of PHT to MRSS and the percentage of the variables in the different MRSS frequency



LIMITED CUTANEOUS SYSTEMIC SCLEROSIS RELATION BETWEEN THE MEAN MRSS AND PULMONARY VARIABLES

Table-9: Relation between the mean MRSS and ILD

ILD	N	Mean	Std. Deviation	P-Value
Absent	14	7.21	2.424	P=0.463
ILD NISIP	12	6.92	3.343	
ILD UIP	5	8.60	2.408	
ILD both	1	4.00	–	
Total	**32**	**7.22**	**2.802**	

Table-10: Relation between the mean MRSS and PFT

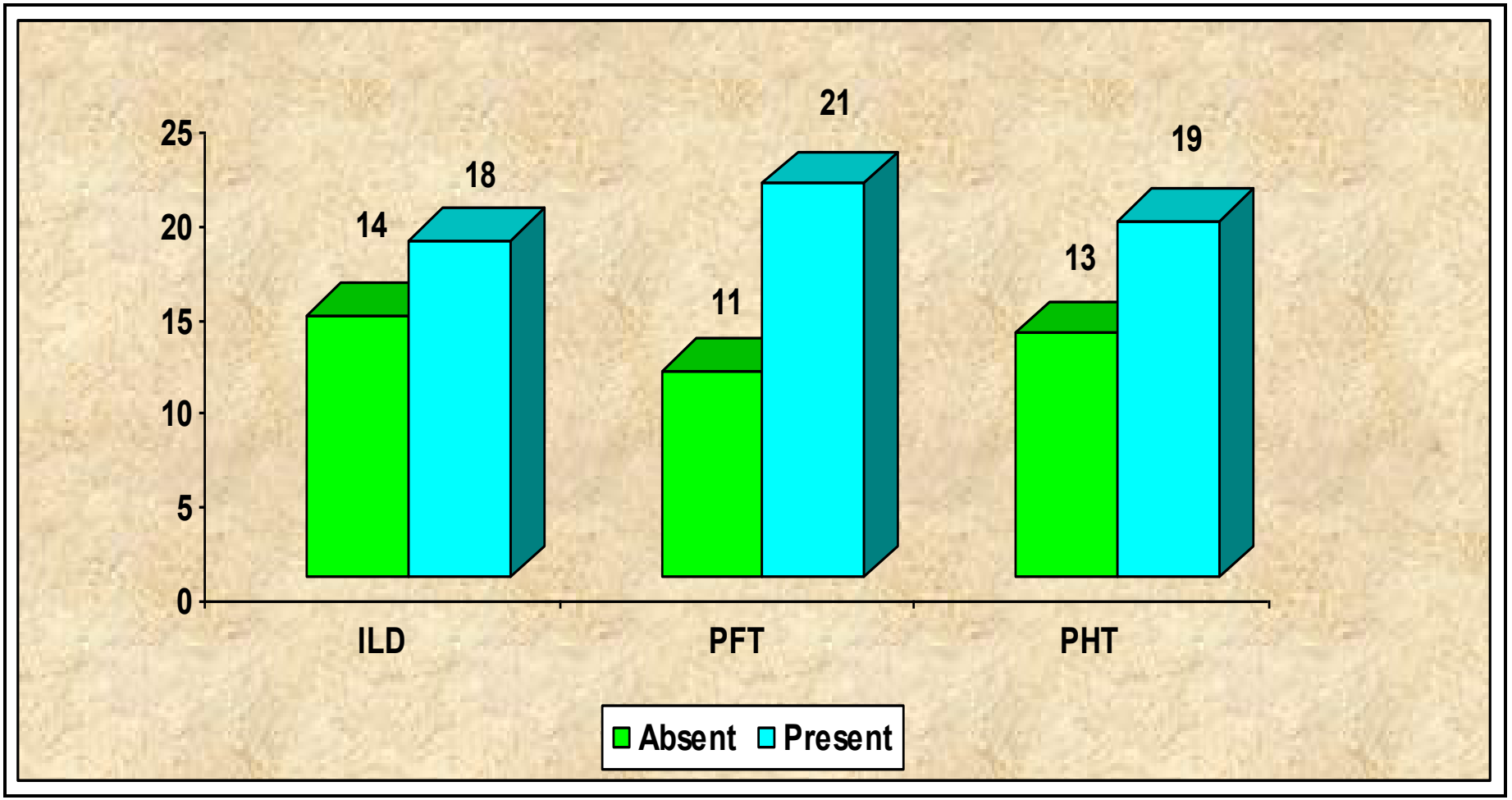
PFT	N	Mean	Std. Deviation	P-Value
Normal	11	6.55	2.018	P=0.333
Reduced	21	7.57	3.124	

Table-11: Relation between the mean MRSS and PHT

	N	Mean	Std. Deviation	P-Value
Normal	13	7.00	2.380	P=0.808
Mild	13	7.62	3.042	
Moderate	6	6.83	3.488	
Total	32	7.22	2.802	

No association seen between the mean MRSS and ILD, PHT reduced PFT in limited cutaneous subtype.

Figure-8: Limited cutaneous Systemic Sclerosis relation between the mean MRSS and Pulmonary Variables



DIFFUSE CUTANEOUS SYSTEMIC SCLEROSIS RELATION BETWEEN THE MEAN MRSS AND PULMONARY VARIABLES

Table-12: Relation between the mean MRSS and ILD

ILD	N	Mean	Std. Deviation	P-Value
Normal	4	20.75	7.455	P=0.046*
ILD NISIP	13	19.38	6.063	
ILD UIP	4	12.00	3.651	
ILD both	2	19.50	2.121	
Total	**23**	**18.35**	**6.228**	

Table-13: Relation between the mean MRSS and PFT

PFT	N	Mean	Std. Deviation	P Value
Normal	2	17.50	7.778	P=0.846
Reduced	21	18.43	6.289	

Table-14:Relation between the mean MRSS and PHT

PHT	N	Mean	Std. Deviation
Absent	19	37.06	.
Mild	1	10.00	.
Moderate	3	17.00	7.810
Total	**23**	**18.35**	**6.228**

Significant association present between mean MRSS and ILD in the diffuse cutaneous type. There was no association with the mean MRSS with PHT and reduced PFT.

Figure-9: Diffuse cutaneous Systemic Sclerosis relation between the mean MRSS and Pulmonary Variables

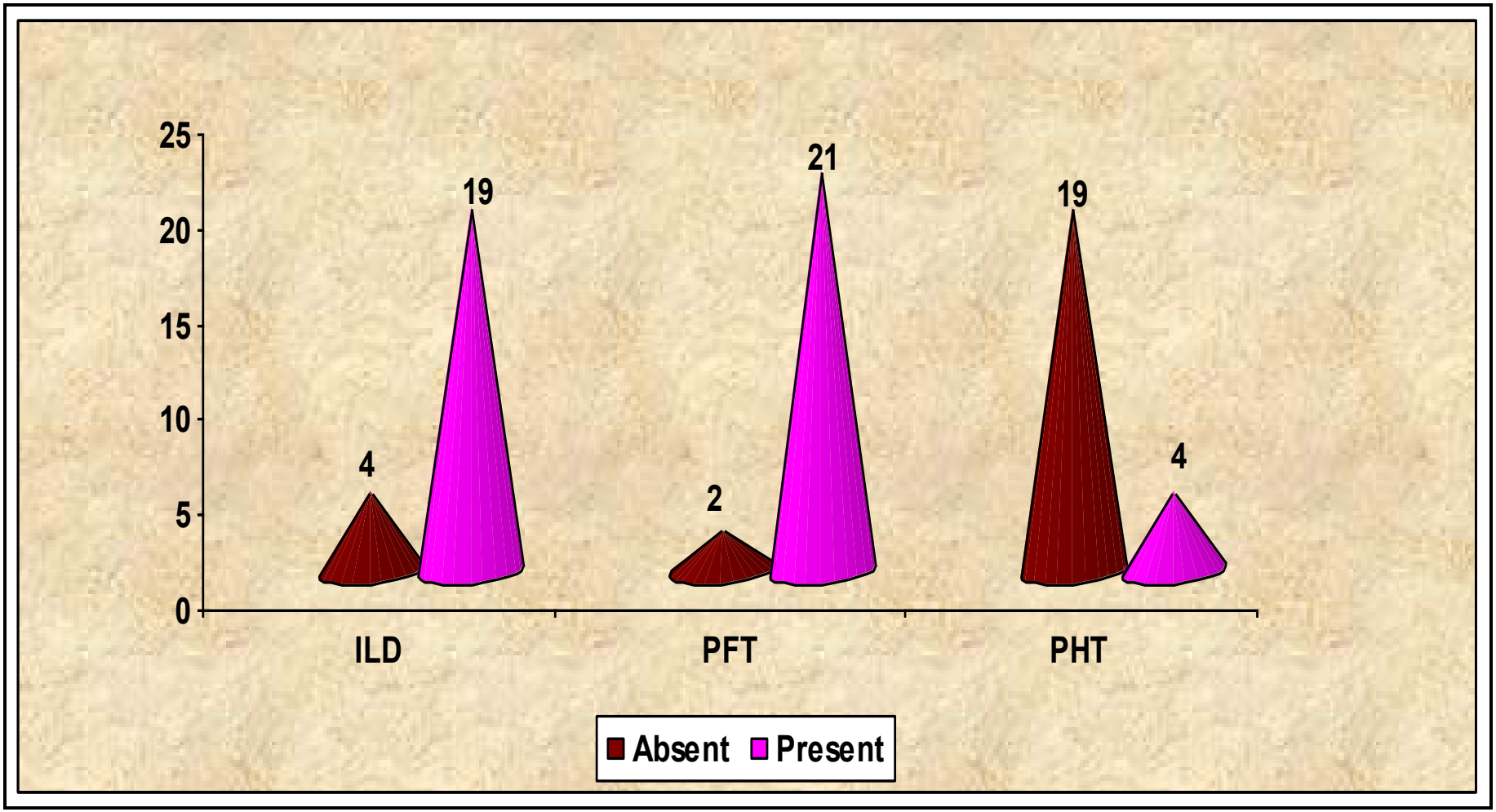
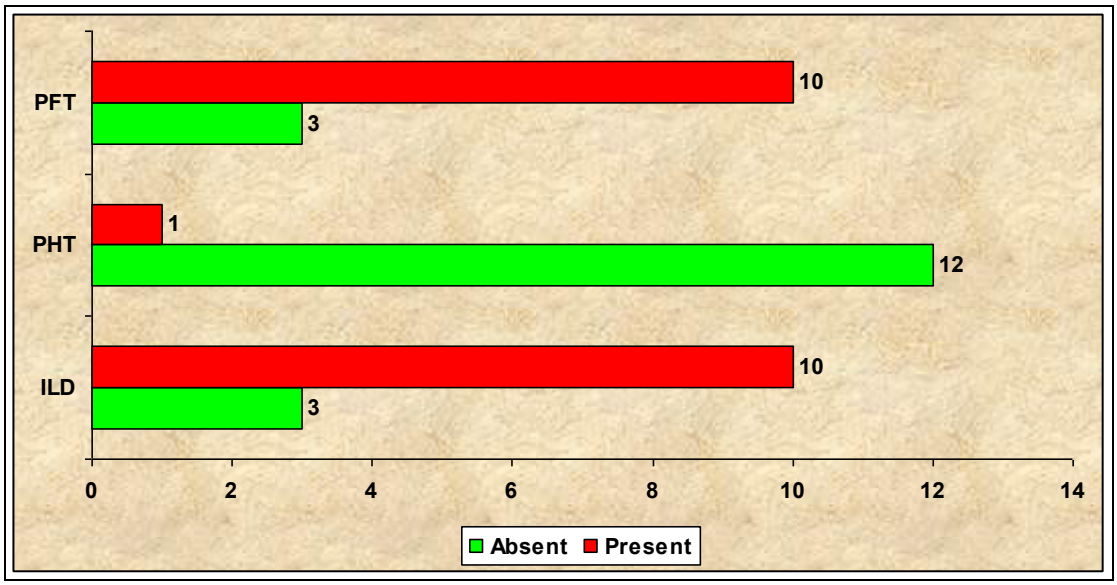


Table-15: Digital Ulcer association with pulmonary variables

Variables	N	Pearson Chi-Square Value	df	P-Value
ILD				
Present	3 (23.1%)	0.914	3	0.822
Absent	10(76.9%)			
PHT				
Absent	12(92.3%)%)	5.860	4	0.210
Present	1 (7.7%)			
PFT				
Normal	3 (23.1%)	0.003 (b)	1	0.637
Reduced	10 (76.9%)			

Figure-10: Digital Ulcer association with pulmonary variables



No association seen between digital ulcer and pulmonary variables.

Table-16: Salt and Pepper association with pulmonary variables

Variables	N	Pearson Chi-Square Value	df	P-Value
ILD				
Absent	12 (31.6%)	0.182 (a)	3	0.980
Present	26 (66.4%			
PHT				
Absent	34 (86.8%)	8.207	4	0.084
Present	4 (10.2%			
PFT				
Normal	8 (21.1%)	0.455	1	0.363
Reduced	30 (78.9%)			

Presence of salt and pepper was not associated with pulmonary variables.

Table-17: Digital Gangrene association with pulmonary variables

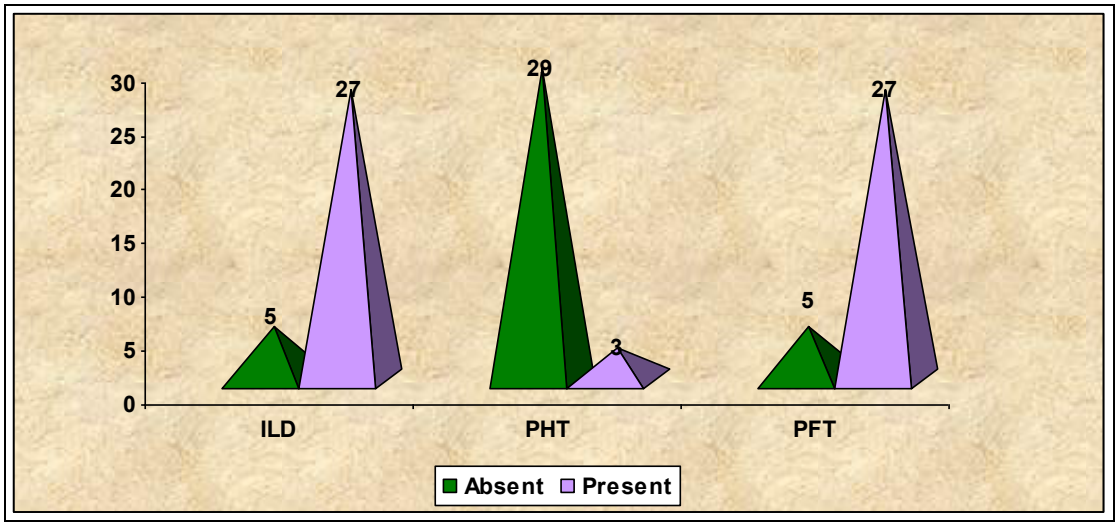
Variables	N	Pearson Chi-Square Value	df	P-Value
ILD				
Absent	2 (25.0%)	1.365 (a)	3	0.714
Present	6 (75.0%)			
PHT				
Absent	8 (100%)	1.832	4	0.767
Present	0 (0%)			
PFT				
Normal	2 (25%)	0.010 (b)	1	0.922
Reduced	6 (75%)			

Digital gangrene was not associated with pulmonary variables.

Table-18: Digital Pitted Scar association with pulmonary variables

Variables	N	Pearson Chi-Square Value	df	P-Value
ILD				
Absent	5 (15.6%)	12.823 (a)	3	0.006*
Present	27 (84.4%)			
PHT				
Absent	29 (90.6%)	2.433 (a)	4	0.657
Present	3 (9.4%)			
PFT				
Normal	5 (15.6%)	2.721	1	0.099
Reduced	27 (84.4%)			

Figure-11: Digital Pitted Scar association with pulmonary variables



Digital pitted scars was significantly associated with ILD. It did not correlate with PHT and reduced PFT.

Table-19: Raynaud's Phenomenon association with pulmonary variables

Variables	N	Pearson Chi-Square Value	df	P-Value
ILD				
Absent	12 (25.5%)	7.944 (a)	3	0.047*
Present	35 (74.5%)			
PHT				
Absent	39 (80.9%)	1.832 (a)	4	0.767
Present	8 (19.1%)			
PFT				
Normal	9 (19.1%)	3.605 (b)	1	0.058
Reduced	38 (80.9%)			

Raynauds Phenomenon was significantly associated with ILD. But there was no association with PHT and reduced PFT.

Table-20: Disease duration with pulmonary variables

Variables	N	Mean	S.D	P.Value
ILD				
Absent	18	3.328	2.728	0.901
Present	37	3.104	2.218	
PHT				
Absent	47	3.291	2.530	0.032*
Present	8	3.000	1.732	
PFT				
Normal	13	3.321	2.624	0.3867
Reduced	42	3.112	2.506	

Disease duration significantly correlated with the PHT. No correlation present between ILD, decreased PFT and disease duration.

DISCUSSION

In our study, out of the total 55 cases there was a female gender predominance 89.1% with males only 10.9%. Similar to this study G.C.Kane et al[77] in their study observed females of 86% and males 14%.

In this study, there was increased frequency of limited cutaneous subtype 32 (58.2%) than the diffuse cutaneous type 23 (41.8%). This was in concurrence with study by Geirsson A J et al[78] with limited and diffuse subtypes of 62% and 38% respectively.

Whereas Ostogic P et al[79] and Terry A. et al[80] showed in their studies diffuse cutaneous type of higher frequency of 58% and 55.6% respectively.

In this study, the median MRSS was 11.8%. Out of the 55 patients 24 (43.6%) were in the 7-15 MRSS range. Similar to this, study by L.G.Hanitsch et al[81] found 58.6% of the patients in the 6-14 MRSS Range.

In our study, pulmonary involvement was seen in 39 cases (70.9%) with ILD by HRCT Chest present in 37 (67.3%) patients. Within the ILD, NSIP pattern 25 (45.5%) was more common than UIP

pattern 9 (16.4%). Similar to this Arroliga et al[82] in their study there was CT evidence of pulmonary fibrosis in 65% of SSc patients.

In a study by Sergio Fernandes et al[83] with 58 SSc patients, 51.7% presented ILD by HRCT Chest whereas ILD by CT scan was seen in 86.7% patients in a study with 45 SSc patients by Ooi GC et al.

Studies by Bouros et al[84] and Veeraraghavan et al[66] showed NSIP pattern was the most prevalent than UIP pattern in SSc associated ILD and NSIP had better prognosis.

In our study, significant association was seen between the MRSS and ILD in the total cases. In the subtypes there was significant association between the mean MRSS and ILD in the diffuse cutaneous type.

Similar to our study L.G.Hanitsch et al[81] showed that higher MRSS was associated with pulmonary fibrosis, digital ulcers and dysphagia in 1483 SSc patients of the German Network registry.

In our study ILD was present in 18 (56%) of limited cutaneous subtype and in 19 (82.6%) of diffuse type which was similar to the study by UA Walker et al, in a meta analysis the occurrence of pulmonary fibrosis was more common in DcSSc 53.4% than limited cutaneous 34.7%[27].

Similarly, Simeon- Aznar et al[85], in the study with 916 Spanish SSc patients, ILD was more frequent in the DcSSc than LcSSc subsets.

Whereas in the study by Kane GC et al, there was no difference in the pulmonary involvement in the two subtypes[77].

A study by Perera A et al[86] in 212 SSc patients ILD was common and equally present in the diffuse and limited subtypes.

The mean MRSS in both limited and diffuse sub types did not correlate with the pulmonary hypertension and reduced pulmonary function.

CXR evidence of ILD was seen in 24 (43.6%) which was similar to the study by Owens G.R. et al with chest X-ray showing pulmonary fibrosis was seen in 40% of the scleroderma patients[59].

Dyspnea was seen in 39 (70.9%) of the cases which was similar to the study by Sergio Fernandes et al[83] were 65.5% of SSc patients had dyspnea.

Decreased pulmonary function was seen in 42 (76.4%) cases in this study. Similar to this study by Owens et al reported 72% of 88 scleroderma patients had decreased pulmonary function.

In a study by Wells A U et al showed 70% of SSc patients with decreased pulmonary function[87].

In this study the disease duration was significantly associated with pulmonary hypertension but there was no association with ILD or reduced PFT.

Similarly in a study by Jerome et al.,[88] increased disease duration was seen in the development of PAH especially in the limited cutaneous type. Studies by Griedinger EL et al[89] and Steen VD et al[61] observed that the onset of pulmonary fibrosis occurred with in the first three years of disease onset in majority of the patients.

In this study PHT was seen in 14.5% similar to the study by Serigo Fernandes et al in which PAH prevalence was seen in 15.3% of the study population[83].

The MRSS was associated with Medsger lung severity score in this study. Similarly Steen and Medsger et al[34] found MRSS correlated with disease severity of organs, especially in the dcSSc.

By BAL, granulocytosis was seen in 9 (23%) of the 36 cases.

Salt and pepper was seen in 38 (69.1%) cases and there was significant association between the MRSS and presence of salt and pepper. Similar to our study, study by Ashish singh et al[90] found that the salt and pepper appearance was seen in 15 out of 16 scleroderma patients and it was a useful marker for early diagnosis of Systemic sclerosis patients.

In a study done in Nigeria by Adelowo OO et al[91], salt and pepper was a common presentation of the skin and it was associated with skin thickening.

In another study by Sharma VK et al[92], 51% of SSc patients had salt and pepper, which was associated with progressive sclerosis.

In this study digital pitted scars were seen in 32 (58.2%) and digital ulcer seen in 13 (23.6%) and there was significant association between digital pitted scars and ILD. There was no association between the digital pitted scars and digital ulcers with pulmonary hypertension and reduced PFT. No association was seen between digital ulcers and ILD in this study.

Similar to this study Sarit Khimdas et al[93] in a study on 938 SSc patients observed digital pitting scars in 53.1% and digital ulcers in 34.1% in the cases.

In their study the digital ulcers and digital pitting scars were associated with ILD, increased MRSS and higher HAQ score.

In another study by Maeda et al[47] digital pitted scars were found in 39% of 87 SSc patients and were associated with skin thickening, Raynauds Phenomenon and joint disease.

Manoussakis MD et al[94] in their study of 34 SSc patients showed the presence of digital pitting scars correlated with impaired pulmonary diffusion and ILD, suggesting that the interstitial pulmonary disease in systemic sclerosis is secondary to vascular pathology like digital pitted scars.

Digital gangrene was seen in 8 (14.5%) in this study, whereas the study by Sarit Khimdas et al observed only 1.8% of digital gangrene in their study group[93].

In our study, Raynauds Phenomenon was seen in 47 (85.5%) and there was association with ILD suggesting vascular pathology in ILD. There was no association between Raynauds phenomenon and pulmonary hypertension or reduced PFT.

The skin biopsy showed early skin lesions in 16% and late fibrotic changes in 83% cases. Study by Frust De et al showed the MRSS as an accurate reflection of the skin biopsy changes and so in this study MRSS was used for correlation[35].

In this study ANA was positive in 44 (80%) cases. As per literature >95% patients of SSc present with autoantibodies. Similar to our study, R.Hesselstrand et al[95] in their study of 276 SSc patients 84% were ANA positive.

CONCLUSION

- In this study on Systemic sclerosis there was a female gender predominance(8:1).
- The limited cutaneous SSc were more than diffuse cutaneous type in this study.
- There was positive correlation between disease duration and PHT.
- 43.6% of the study group were in the 7-15 MRSS Range.
- Presence of salt and pepper had significant association with MRSS in this study.
- Dyspnea was the most common respiratory symptom and it correlated positively with MRSS.
- The MRSS was significantly associated with presence of ILD in the study group.
- ILD was more common in diffuse cutaneous type and the mean MRSS was significantly associated with ILD in diffuse cutaneous type.

- There was no association between MRSS and PHT in this study.
- There was significant association between MRSS and the Medsger disease severity of lung.
- Digital pitted scars and Raynaud's Phenomenon positively correlated with ILD in this study group.
- ANA positivity was seen in 80% of the cases.

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"A STUDY ON CLINICO IMMUNO PATHOLOGICAL CORRELATION OF SKIN AND PULMONARY INVOLVEMENT IN SYSTEMIC SCLEROSIS"

Dissertation Submitted to

THE TAMIL NADU DR.M.G.R.MEDICAL UNIVERSITY,
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In partial fulfillment of the regulation
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BRANCH - IX

MADRAS MEDICAL COLLEGE
RAJIV GANDHI GOVERNMENT GENERAL HOSPITAL
CHENNAI – 600 003.

AUGUST 2013

CERTIFICATE

This is to certify that this dissertation entitled "**A STUDY ON CLINICO IMMUNO PATHOLOGICAL CORRELATION BETWEEN SKIN AND PULMONARY MANIFESTAIONS IN SYSTEMIC SCLEROSIS**" presented here is original work done by **Dr.T.AARTHI PRIYA**, DM Post Graduate in the Department of Rheumatology, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai- 600003 in partial fulfillment of the university rules and regulation for the award of D.M. Branch IX- Rheumatology, under my guidance and supervision during the academic period from 2010-2013.

Dr.V.KANAGASABAI, MD.,
Dean,
Madras Medical College and
Rajiv Gandhi Govt. General Hospital,
Chennai – 600 003.

Dr.S.RUKMANGATHARAJAN, MD., DM., FMMC.,
Professor and HOD,
Department of Rheumatology,
Madras Medical College and
Rajiv Gandhi Govt. General Hospital,
Chennai – 600 003.

DECLARATION

I, **Dr.T.AARTHI PRIYA** hereby solemnly declare that this dissertation entitled **"A STUDY ON CLINICOIMMUNO PATHOLOGICAL CORRELATION BETWEEN SKIN AND PULMONARY MANIFESTAIONS IN SYSTEMIC SCLEROSIS"** was done by me in the Department of Rheumatology, Madras Medical College & Rajiv Gandhi Govt. General Hospital, Chennai-3 during July 2011 to February 2013 under the guidance and supervision of Prof.Dr.S.Rukmangatharajan, MD., DM., FMMC., This dissertation is submitted to the Tamil Nadu Dr.M.G.R.Medical University towards the partial fulfillment of requirement for the award of D.M., Degree in Rheumatology.

Signature of the Candidate

Date :
Place :

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INDEX

ABBREVIATIONS

SSc	:	Systemic Sclerosis
DcSSc	:	Diffuse Cutaneous Systemic Sclerosis
LcSSc	:	Limited Cutaneous Systemic Sclerosis
MMP-12	:	Matrix Metalloproteinase-12
MHC	:	Major Histocompatability complex
TCR	:	T Cell Receptor
PTPN	:	Protein Tyrosine Phosphatase
NSIP	:	Non Specific Interstitial Pneumonitis
UIP	:	Usual Interstitial pneumonitis
VCAM	:	Vascular cell adhesion molecule
VEGF	:	Vascular Endothelial growth factor
PDGF	:	Platelet derived growth factor
PAH	:	Pulmonary arterial hypertension
ACA	:	Anti centromere Antibody

AECA	:	Anti endothelial cell antibodies
ANA	:	Anti Nuclear Antibody
MRSS	:	Modified Rodnan skin score
EULAR	:	European League against Rheumatism
ILD	:	Interstitial lung disease
FVC	:	Forced vital capacity
FEV1	:	Forced expiratory volume in 1 sec.
HRCT	:	High resolution computed tomography
PFT	:	Pulmonary function test
GGO	:	Ground glass opacity
BAL	:	Broncho alveolar lavage
PAP	:	Pulmonary arterial pressure
DL co	:	Diffusion capacity of carbon monoxide

APPENDIX – 1

Assessment of disease severity and prognosis in SSc/T.A.Medsger Jr. et al.,

Table II. Revised preliminary SSc severity scale

Organ system	0 (normal)	1 (mild)	2 (moderate)	3 (severe)	4 (endstage)
1. General	**Wt loss < 5%; PCV 37.0%+; Hb 12.3+ Gm/dl**	**Wt loss 5.0-9.9%; PCV 33.0-36.9% Hb 11.0-12.2 Gm/dl**	**Wt loss 10.0-14.9%; PCV 29.0-32.9% Hb 9.7-10.9 Gm/dl**	**Wt loss 15.0-19.9%; PCV 25.0-28.9% Hb 8.3-9.6 Gm/dl**	**Wt loss 20+ %; PCV < 25.0% Hb < 8.3 Gm/dl**
2. Peripheral vascular	**No Raynaud's; Raynaud's not requiring vasodilators**	Raynaud's requiring vasodilators	Digital pitting scars	Digital tip ulcerations	Digital gangrene
3. Skin	TSS 0	TSS 1-14	TSS 15-29	TSS 30-39	TSS 40+
4. Joint/tendon	FTP 0-0.09 cm	FTP 1.0-1.9 cm	FTP 2.0-3.9 cm	FTP 4.0-4.9 cm	FTP 5.0+ cm
5. Muscle	Normal proximal muscle strength	Proximal weakness, mild	Proximal weakness, moderate	Proximal weakness, severe	**Ambulation aids required**
6. GI tract	**Normal esophagram; normal small bowel series**	Distal esophageal hypoperistalsis; small bowel series abnormal	Antibiotics required for bacterial over-growth	Malabsorption syndrome; episodes of pseudo-obstruction	Hyperalimentation required
7. Lung	**DLCO 80+%; FVC 80+%; No fibrosis on radiograph; sPAP < 35 mmHg**	**DLCO 70-79%; FVC 70-79%; basilar rales; Fibrosis on radiograph sPAP 35-49 mmHg**	**DLCO 50-69%; FVC 50-69%; sPAP 50-64 mmHg**	**DLCO < 50%; FVC < 50%; sPAP 65+ mmHg**	**Oxygen required**
8. Heart	**EKG normal; LVEF 50+%**	**EKG conduction defect; LVEF 45-49%**	**EKG arrhythmia; LVEF 40-44%**	**EKG arrhythmia requiring Rx; LVEF 30-40%**	**CHF; LVEF < 30%**
9. Kidney	**No Hx SRC with serum creatinine < 1.3 mg/dl**	**Hx SRC with serum creatinine < 1.5 mg/dl**	**Hx SRC with serum creatinine 1.5-2.4 mg/dl**	**Hx SRC with serum creatinine 2.5-5.0 mg/dl**	**Hx SRC with serum creatinine > 5.0 mg/dl or dialysis required**

Wt: weight; PCV: packed cell volume (hematocrit); Hb:hemoglobin; TSS:total skin thickness score; FTP: fingertip-to-palm distance in flexion; DLCO: diffusing capacity for carbon monoxide, % predicted; FVC: forced vital capacity, % predicted; sPAP:estimated pulmonary artery systolic pressure by Doppler echo; EKG:electrocardiogram; LVEF:left ventricular ejection fraction; Rx:treatment; CHF:congestive heart failure; Hx:history of; SRC:scleroderma renal crisis.

N.B. If two items are included for a severity grade, only one is required for the patient to be scored as having that severity level.

Introduction

Aims and Objectives

Review of Literature

Materials and Methods

Results of the Data

Discussion

Conclusion

Bibliography

Annexure

A STUDY ON "THE CLINICO IMMUNO PATHOLOGICAL CORRELATION OF SKIN AND PULMONARY INVOLVEMENT IN SYSTEMIC SCLEROSIS"

Name: Age: Sex: Date:

Address:

D.O.E. RCC No.

H/o. Present Illness:

Past History:

Family History:

Personal History:

Treatment History:

General Examination

Pallor: Icterus: Cyanosis:

Clubbing: Lymphadenopathy: Pedal Edema:

Skin:

Nails:

Hair:

Pulse: BP:

Systemic Examination

Cardiovascular System: Respiratory System:

Abdomen: Central Nervous System:

Musculoskeletal System Examination:

INVESTIGATION

Haemogram

Hb: TC: DC:

Platelet: ESR:

Immunological

ANA: CRP:

Bio-Chemistry

Blood

Sugar: Urea: Creatinine:

Bilirubin: AST: ALT:

ALP: Total Proteins: Albumin:

Lipid profile:

Urine Routine:

Pulmonary function tests

Radiography

1. Chest X-ray 2. HRCT

Referrals

1. Dermatology
2. Radiology
3. Thoracic Medicine
4. Cardiology

S. No	RCC No	Age/ Sex	Sex	Type SSC		Disease Duration	MRSS	Salt + Pepper	Digital Ulcer	Digital Pits/ Scar	Gangrene	Dysnea	Echo	ECG Changes	Cx R E/O ILD	HRCT Chest	PFT Restrictive	DLCO	ANA	SCL 70	Skin Biopsy Early/ Late Changes	BAL	Raynaud's	Disease Severity Medsger	
				LC	DC																			Skin	Lung
1	48172	43	F		DC	10 Y	18	+	+	+	-	Gr.III	Cone LVH	+	+	ILD (NSIP+UIP)	R	N	N	N	Late	P	+	2	3
2	49938	32	F	LC		5 Y	6	-	-	-	-	Absent	N	-	-	N	N	N	P	-	Late	-	+	1	0
3	52203	38	F	LC		1 Y	6	-	+	-	-	Gr.III	Mild PHT	-	-	ILD (NSIP)	R	Decreased	P	N	Early	P	+	1	1
4	52265	45	F		DC	4 Y	8	+	-	-	-	Gr.III	Moderate PHT	+	+	ILD (UIP)	R	Decreased	P	P	Late	P	+	1	2
5	52470	36	F	LC		5 Y	6	-	+	+	+	Absent	N	-	-	N	N	N	N	N	Late	-	+	1	0
6	53744	30	F	LC		6 Y	10	+	-	-	-	Absent	N	-	-	N	N	N	N	-	Late	-	+	1	0
7	53842	30	F	LC		10 Y	6	+	-	-	-	Absent	N	-	-	N	N	Decreased	N	N	Late	-	+	1	0
8	53762	40	F		DC	5 Y	10	+	-	-	-	Gr.II	N	-	+	ILD (NSIP)	R	N	P	N	Late	-	+	1	1
9	53884	21	F	LC		6 M	4	-	-	-	-	Gr.II	N	-	+	ILD (NSIP)	R	Decreased	P	N	Late	-	+	1	1
10	53842	36	F		DC	2 Y	19	+	-	-	-	Gr.III	N	-	Rt. Lzopacity	Pneumonitis Rt LL	R	Decreased	P	N	Late	P	+	2	1
11	53854	35	F	LC		7 Y	12	-	+	+	-	Gr.III	N	-	+	ILD (UIP)	R	Decreased	P	-	Late	P	+	1	2
12	53829	43	F		DC	3 Y	10	-	-	+	-	Gr.III	Mild PHT	+	+	ILD (UIP)	R	Decreased	P	-	Late	P	+	1	2
13	53837	28	F	LC		1.6 Y	4	+	+	+	-	-	N	-	-	N	N	N	P	-	Late	-	+	1	0
14	53732	30	F	LC		3 Y	8	-	-	+	-	+	N	-	-	N	N	N	N	-	Late	-	+	1	0
15	53744	46	F		DC	6 Y	27	+	-	+	-	Gr.III	N	-	+	ILD (NSIP)	R	Decreased	P	P	Late	P	+	2	2
16	54305	21	F	LC		6 M	4	-	-	-	-	Gr.II	N	-	-	ILD (NSIP)	R	Decreased	P	N	Late	P	+	1	1
17	54074	37	F	LC		1.6 Y	4	-	-	+	-	Gr.III	Severe PHT	+	-	ILD (NSIP)	R	Decreased	P	N	Late	Not Done	+	1	2
18	54252	30	F	LC		5 M	7	+	-	+	-	Gr.III	N	-	+	ILD (UIP)	R	Decreased	P	N	Late	P	+	1	2
19	54498	30	F	LC		4M	10	+	-	-	-	Gr.III	Severe PHT	+	Dilahht Rt. PA	N	R	Decreased	P	N	Late	Not Done	+	1	2
20	54599	28	F		DC	3.6Y	12	+	-	+	-	Gr.II	N	-	-	ILD (NSIP)	R	Decreased	P	N	Late	-	+	1	1
21	54922	25	F	LC		6M	8	+	-	-	-	-	N	-	-	N	N	N	P	N	Early	-	+	1	0
22	55045	35	F	LC		8M	10	+	-	-	-	Gr.II	N	-	-	ILD (UIP)	R	Decreased	P	N	Early	P	+	1	1
23	55065	48	F	LC		10Y	+	-	+	+	+	Gr.III	N	RBBB +	+	ILD (NSIP)	R	Decreased	N	N	Late	-	+	1	2

S. No	RCC No	Age/ Sex	Sex	Type SSC		Disease Duration	MRSS	Salt + Pepper	Digital Ulcer	Digital Pits/ Scar	Gangrene	Dysnea	Echo	ECG Changes	Cx R E/O ILD	HRCT Chest	PFT Restrictive	DLCO	ANA	SCL 70	Skin Biopsy Early/ Late Changes	BAL	Raynaud's	Disease Severity Medsger	
				LC	DC																			Skin	Lung
24	55069	56	F		DC	1Y	12	+	-	-	-	-	N	N	N	N	N	D	P	N	Early	-	-	1	0
25	54250	56	F		DC	5Y	13	+	-	+	-	Gr.II	N	+	+	ILD (NSIP)	R	D	N	N	Late	P	+	1	1
26	54510	38	F	LC		7M	4	-	-	-	-	-	N	-	N	N	N	N	P	N	Early	Not Done	-	1	0
27	55135	28	F	LC		1Y	4	-	-	-	-	Gr.III	Severe PHT	+	+	NSIP+ UIP	R	Decreased	P	N	Late	Not Done	+	1	2
28	55179	45	F	LC		5 Y	8	-	-	-	-	Gr.II	N	-	N	ILD (NSIP)	R	Decreased	P	N	Late	P	+	1	1
29	55272	45	F		DC	8M	22	+	-	-	-	Gr.I	N	N	N	N	R	N	N		Early	-	-	2	0
30	54382	38	M		DC	6M	28	+	-	+	-	Gr.II	N	N	N	ILD (NSIP)	R	Decreased	P	N	Early	P	+	2	1
31	54612	49	M		DC	1 Y	21	+	-	-	-	Gr.IV	Mod PHT	Old ASMI	+	ILD (NSIP+UIP)	R	Decreased	P	P	Late	P	+	2	3
32	55214	48	M		DC	2 Y	24	+	-	+	-	Gr.II	N	-	+	ILD (NSIP)	R	Decreased	P	N	Late	P	+	2	1
33	55176	36	M	LC		8 Y	10	+	+	+	-		N	N	-	ILD (NSIP)	R	Decreased	P	N	Late	-	+	1	1
34	55571	43	F		DC	1 Y	22	+	-	+	-	Gr.II	Mod PHT	+	+	ILD (NSIP)	R	Decreased	P	N	Late	P	+	2	2
35	55627	35	F	LC		4 Y	12	+	-	-	-	-	N	-	-	N	R	N	P	N	Late	-	+	1	0
36	55015	32	F		DC	1.6 Y	19	+	-	+	-	-	N	-	-	ILD (NSIP)	R	N	N	N	Early	P	+	2	1
37	55695	35	F		DC	1 Y	23	+	-	+	-	Gr.II	N	-	-	ILD (NSIP)	-	N	P	N	Late		+	2	1
38	55778	42	M		DC	5Y	16	+	-	+	+	Gr.III	N	-	+	ILD (UIP)	R	Decreased	P	N	Late	P	+	2	2
39	55790	22	F	LC		2 Y	8	+	-	-	-	-	-	-	-	N	N	N	P	N	Late	-	-	1	0
40	54896	49	F	LC		2 Y	6	+	-	-	-	Gr.II	N	-	-	ILD (NSIP)	R	Decreased	N	N	Late	-	+	1	1
41	54641	38	F	LC		7 Y	4	+	+	+	+	-	N	-	-	N	N	N	N	N	Late	-	+	1	0
42	54321	30	F	LC		2 Y	8	+	+	+	-	Gr.II	N	-	-	ILD (UIP)	R	Decreased	P	N	Late	P	+	1	1
43	54412	41	F	LC		2 Y	10	+	+	+	-	Gr.II	N	-	+	ILD (NSIP)	R	N	N	N	Late	-	+	1	1
44	55460	40	F		DC	5 Y	12	+	+	+	+	Gr.II	N	-	+	ILD (NSIP)	R	Decreased	P	N	Late	-	+	1	1
45	55517	29	F		DC	3 Y	17	+	+	+	+	Gr.III	N	-	+	ILD (NSIP)	R	Decreased	P	N	Late	-	+	2	2
46	55652	32	F		DC	6 M	14	+	-	+	-	Gr.III	N	+	+	ILD (UIP)	R	Decreased	P	N	Early	P	+	1	2

S. No	RCC No	Age/ Sex	Sex	Type SSC		Disease Duration	MRSS	Salt + Pepper	Digital Ulcer	Digital Pits/ Scar	Gangrene	Dysnea	Echo	ECG Changes	Cx R E/O ILD	HRCT Chest	PFT Restrictive	DLCO	ANA	SCL 70	Skin Biopsy Early/ Late Changes	BAL	Raynaud's	Disease Severity Medsger	
				LC	DC																			Skin	Lung
47	50914	30	F		DC	4 Y	30	+	-	+	-	Gr.I	-	-	-	Atelectasis	R	Decreased	N	N	Late	-	+	3	1
48	55812	25	F	LC		1 Y	15	+	-	+	-	Gr.II	N	-	+	ILD (NSIP)	R	Decreased	N	N	Late	-	+	2	1
49	50145	23	F	LC		2 Y	6	-	-	+	-	Gr.I	N	-	+	ILD (UIP)	R	Decreased	N	N	Late	P	-	1	1
50	56035	38	F		DC	4 Y	24	+	+	+	+	Gr.III	N	-	+	ILD (NSIP+UIP)	R	Decreased	P	P	Late	P	+	2	2
51	56049	20	F	LC		8 M	8	-	-	-	-	-	N	-	N	N	N	N	N	N	Late	-	-	1	0
52	56120	36	F	LC		3 Y	6	+	-	+	+	Gr.II	N	-	+	ILD (NSIP)	R	Decreased	P	N	Late		+	1	1
53	560142	31	F	LC		2 Y	6	-	-	+	-	Gr.I	N	-	N	ILD (NSIP+UI	R	Decreased	P	N	Late	-	+	1	1
54	56210	26	F	LC		6 Y	7	-	-	-	-		N	+	N	N	R	N	P	N	Late	-	-	1	0
55	55312	30	M		DC	3 Y	21	+	-	+	-	Gr.III	N	-	+	ILD (NSIP)	R	Decreased	P	N	Late	P	-	2	2

PATIENT CONSENT FORM

Study Details: **A study on clinico immuno pathological correlation of skin and pulmonary involvement in systemic sclerosis**

Study Centre: Department of Rheumatology,
Rajiv Gandhi Government General Hospital,
Madras Medical College, Chennai-600 003.

Patient may check (✓) these boxes

I confirm that I have read and understood the Information Sheet for the above study. I have- had the opportunity to ask questions and all my questions and doubts have been answered to my complete satisfaction. ☐

I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my legal rights being affected. ☐

I understand that the Clinical study personnel, the Ethics Committee and the Regulatory Authorities will not need my permission to look at my health records both in respect to the current study and any further research that may be conducted in relation to it, even if I withdraw from the study. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ☐

I agree to take part in the above study and to comply with the instructions given during the study and to faithfully co-operate with the study team, and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ☐

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological, biochemical, radiological tests. ☐

I hereby consent to participate in this study. ☐

Signature of Investigator Thumb Impression of Patient

Patient Name/ Address

Name of the Investigator

<u>ஆராய்ச்சி ஒப்புதல் படிவம்</u>

ஆராய்ச்சி தலைப்பு

சிஸ்டமிக் ஸ்கிரோசிஸ் (Systemic Sclerosis) ஆராய்சி பற்றிய ஒப்பிடுதல்

ஆராய்ச்சி நிலையம் : முடக்குவாதவியல் துறை,
இராஜீவ் காந்தி அரசு பொது மருத்துவமனை,
சென்னை மருத்துவக் கல்லூரி, சென்னை – 03.

பங்கு பெறுவரின் பெயர் :
பாலினம் :
பங்குபெறபவரின் எண் :

பங்கு பெறுபவர் இதனை (✓) குறிக்கவும்

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. என்னுடைய சந்தேகங்களை கேட்கவும், அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டது. ☐

நான் இவ்வாய்வில் தன்னிச்சையாகதான் பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும் எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்து கொண்டேன். ☐

இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்த மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். நான் ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன். ☐

இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களையும், பரிசோதனை முடிவுகளையும் மற்றும் சிகிச்சை தொடர்பான தகவல்களையும் மருத்துவர் மேற்கொள்ளும் ஆய்வில் பயன்படுத்திக்கொள்ளவும் அதை பிரசுரிக்கவும் என் முழு மனதுடன் சம்மதிக்கின்றேன். ☐

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக்கொள்கிறேன். எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின்படி நடந்து கொள்வதுடன் இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்று உறுதியளிகிறேன். எனது உடல் நலம்பாதிக்கப்பட்டாலோ அல்லது எதிர்பாராத வழக்கதிற்கு மாறான நோய்க்குறி தென்பட்டாலோ உடனே அதை மருத்து அணியிடம் தெரிவிப்பேன் என உறுதி அளிக்கிறேன். ☐

பங்கேற்பவரின் கையொப்பம்..... இடம்.....

தேதி..... கட்டைவிரல் ரேகை

பங்கேற்பவரின் பெயர் மற்றும் விலாசம்

.....

ஆய்வாளரின் கையொப்பம் ..... இடம்.....

தேதி..... ஆய்வாளரின் பெயர் .....

<u>ஆராய்ச்சி தகவல் தாள்</u>

சென்னை இராஜீவ்காந்தி அரசு பொது மருத்துவனையில் சிஸ்டமிக் ஸ்கிரோசிஸ் (Systemic Sclerosis) ஆராய்சி இங்கு நடைபெற்று வருகிறது.

நீங்களும் ஆராய்ச்சியில் பங்கேற்க விரும்புகிறோம். இந்த ஆராய்ச்சியில் உங்களை பங்கேற்க வைத்து அதன் தகவல்களை ஆராய்வோம் அல்லது உங்கள் இரத்தத்தை பரிசோதனைக்கு உட்படுத்தி ஆராய்வோம். அதனால் தங்களின் நோயின் ஆய்வறிக்கையோ, சிகிச்சைக்கோ பாதிப்பு ஏற்படாது என்பதை தெரிவித்துக்கொள்கிறோம்.

முடிவுகளை அல்லது கருத்துகளை வெளியிடும்போதோ அல்லது ஆராய்ச்சியின் போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிடமாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த சிறப்பு பரிசோதனைகளின் முடிவுகளையும் நோயின் தன்மை பற்றியும் ஆராய்ச்சியின்போது அல்லது ஆராய்ச்சியின் முடிவின் போது தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில் தான் இருக்கிறது. மேலும் நீங்கள் எந்நேரமும் இந்த ஆராய்ச்சியிலிருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

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ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

தேதி:

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No: 04425305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. T. Aarthi Priya. M.D
PG in DM Rheumatology
Madras Medical College, Chennai -3

Dear Dr. T. Aarthi Priya. M.D

The Institutional Ethics Committee of Madras Medical College reviewed and discussed your application for approval of the proposal entitled "The Clinico-Immuno Pathological correlation of skin and pulmonary involvement in Systemic Sclerosis" No. 14062011.

The following members of Ethics Committee were present in the meeting held on 24.06.2011 conducted at Madras Medical College, Chennai -3.

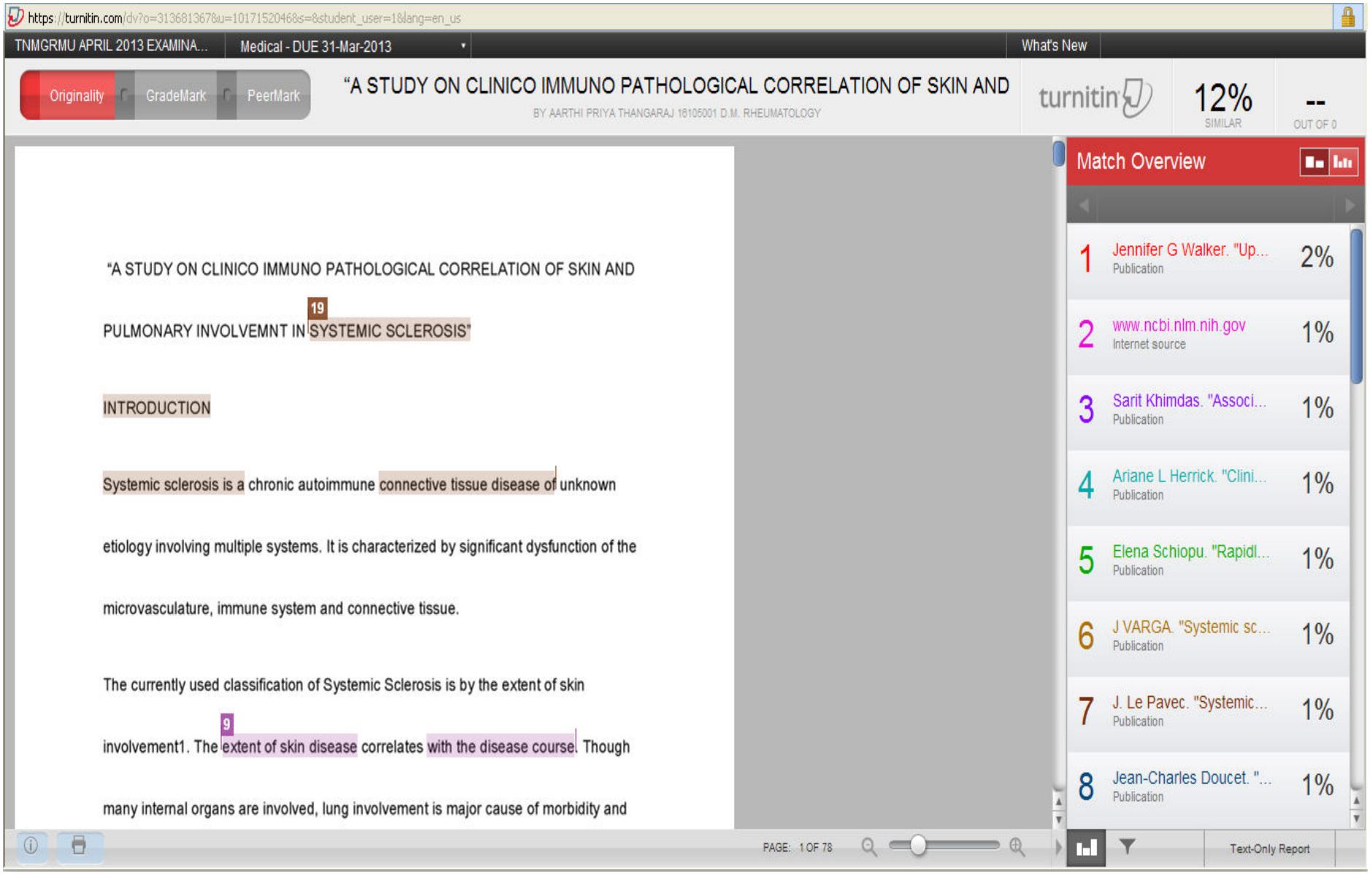
1.	Prof. S.K. Rajan, MD	-- Chairperson
2.	Prof. V. Kanagasabai MD Dean, Madras Medical College, Chennai-3,	-- Deputy chairman
3.	Prof. A. Sundaram, MD Vice Principal , Madras Medical College, Chennai -3	-- Member Secretary
4.	Prof R. Sathianathan MD	-- Member
5.	Prof R. Nandhini, MD Director, Institute of Pharmacology, MMC, Ch-3	-- Member
6.	Prof. Geetha Subramanian MD DM Prof & Head , Dept. of Cardiology, MMC, Ch-3	-- Member
7.	Prof. Pregna B. Dolia MD Director , Institute of Biochemistry, MMC, Ch-3	-- Member
8.	Prof. C. Rajendiran .MD Director , Institute of Internal Medicine, MMC, Ch-3	-- Member
9.	Thiru. A. Ulaganathan Administrative Officer, MMC, Chennai -3	-- Layperson
10.	Thiru. S. Govindasamy . BA.BL	-- Lawyer
11.	Tmt. Arnold Soulina	-- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd /. Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information / informed consent and asks to be provided a copy of the final report

Member Secretary, Ethics Committee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INTRODUCTION
Systemic sclerosis is a chronic autoimmune connective tissue disease of unknown
etiology involving multiple systems. It is characterized by significant dysfunction of the
microvasculature, immune system and connective tissue.
The currently used classification of Systemic Sclerosis is by the extent of skin
involvement1. The extent of skin disease correlates with the disease course. Though
many internal organs are involved, lung involvement is major cause of morbidity and
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“A STUDY ON CLINICO IMMUNO PATHOLOGICAL CORRELATION OF SKIN AND PULMONARY INVOLVEMNT IN SYSTEMIC SCLEROSIS” INTRODUCTION Systemic sclerosis is a chronic autoimmune connective tissue disease of unknown etiology involving multiple systems. It is characterized by significant dysfunction of the microvasculature, immune system and connective tissue. The currently used classification of Systemic Sclerosis is by the extent of skin involvement1. The extent of skin disease correlates with the disease course. Though many internal organs are involved, lung involvement is major cause of morbidity and mortality in SSC. While some studies regard skin involvement as a surrogate marker for pulmonary...