"A STUDY ON QT INTERVAL IN PATIENTS WITH SLE AND ITS CORRELATION WITH DISEASE ACTIVITY AND AUTO ANTIBODIES"

Dissertation Submitted to

THE TAMIL NADU DR.M.G.R.MEDICAL UNIVERSITY,
CHENNAI- 600 032.

In partial fulfillment of the regulation
for the award of the degree of

DM (RHEUMATOLOGY)
BRANCH - IX

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

AUGUST 2014

CERTIFICATE

This is to certify that this dissertation "**A study on QT interval in patients with SLE and its correlation with disease activity and auto antibodies"** presented here is the original work done by Dr.S.Sham, D.M Postgraduate in the Department of Rheumatology, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai 600003 in partial fulfilment 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 2011-2014.

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DECLARATION

I, Dr.S.SHAM hereby solemnly declare that this dissertation entitled "**A study on QT interval in patients with SLE and its correlation with disease activity and auto antibodies"** was done by me in the Department of Rheumatology, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai 600003 during January 2012 to December 2013 under the guidance and supervision of Dr.S.Rajeswari M.D.,D.M. This dissertation is submitted to the Tamil Nadu Dr.M.G.R.Medical University towards the partial fulfilment of requirement for the award of D.M. degree in Rheumatology.

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ACKNOWLEDGEMENT

I express my heartful gratitude to the **Dean, Dr.R.Vimala M.D.** Madras Medical College & Rajiv Gandhi Govt. General Hospital, Chennai-3 for permitting me to do this study.

I gratefully acknowledge and sincerely thank **Dr.S.Rajeswari, M.D.,D.M**. Professor and Head Department of Rheumatology, for her valuable suggestions, guidance, constant supervision and moral support without which this study would not have been possible.

I am thankful to **Dr.J.Euphrasia Latha, M.D.,**Additional Professor for her valuable guidance in doing the Immunological and Biochemical workup of patients.

I express my gratitude to **Dr.T.N.Tamilselvam, M.D,D.M.,** Asst.Professor, Department of Rheumatology for the valuable guidance, advice and suggestions during this study.

I am extremely thankful to Assistant Professors **Dr.R.Ravichandaran M.D.,DCH,D.M., Dr.S.Balameena M.D.,DCH,D.M.,** and **Dr.Theresa Mary M.D.,DCH,** and my fellow postgraduates for their constant support and advice during this study.

I am extremely thankful to the **Laboratory personnel** for their invaluable help in carrying out the immunological investigations without which, this work would not have been possible.

I thank the **Physiotherapist, all Staff Nurses** and **all the Paramedical staff members** in Department of Rheumatology Madras Medical College & Rajiv Gandhi Govt. General Hospital, Chennai for their full cooperation in conducting this study.

I thank my parents, my wife and my daughter for their understanding and co-operation in completion of this work.

Last but not the least, I owe my sincere gratitude to the patients and their relatives who co-operated for this study, without whom the study could not have been possible.

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ABBREVIATIONS USED

SLE – Systemic Lupus Erythematosus

ESR – Erythrocyte Sedimentation Rate

CLASI - Cutaneous Lupus Erythematosus Disease Area and Severity Index

SLEDAI – Systemic Lupus Erythematosus Disease Activity Index

ANA – Antinuclear Antibody

Anti ds DNA – Anti Double Stranded Deoxy Ribo Nucleic Acid

ELISA – Enzyme Linked Immunosorbent Assay

CD – Cluster of Differentiation

IL – Interleukin

CTLA 4 - Cytotoxic T lymphocyte associated molecule

NET – Neutrophil Extracellular Trap

CVS – Cardiovascular System

ECG – Electrocardiograph

ECHO – Echocardiogram

CXR – Chest X Ray

MRI – Magnetic Resonance Imaging

TMB – Tetra methyl benzidine

PBS – Phosphate Buffer Solution

FITC – Fluorescein iso thiocyanate

SPECT – Single Photon Emission Computed Tomography

BILAG - British Lupus Isles Assessment Group Index

SLEDAI - Systemic Lupus Erythematosus Disease Activity Index

SELENA – Safety of Estrogen in Lupus Erythematosus National Assessment Trial

SLAM – Systemic Lupus Activity Measure

LAI - The Lupus Activity Index

ECLAM- The European Consensus Lupus Activity Measurement Index

SFI - Selena SLEDAI Flare Index

RIFLE – Responder Index For Lupus Erythematosus

SRI 50 – SLEDAI 2K Responder Index

HCQ – Hydroxychloroquine

NSAID'S – Non steroidal anti inflammatory drugs

NT pro BNP – N terminal pro Brain Natriuretic Peptide

INDEX

S.NO	CONTENTS	PAGE NO.
1.	INTRODUCTION	1
2.	AIM OF THE STUDY	3
3.	REVIEW OF LITERATURE	4
4.	MATERIALS AND METHODS	33
5.	RESULTS AND ANALYSIS	40
6.	DISCUSSION	63
7.	CONCLUSION	71
8.	BIBLIOGRAPHY	
9.	ANNEXURE A) PROFORMA (A1), SLEDAI (A2) & CLASI (A3) B) MASTER CHART C) PATIENT CONSENT FORM AND INFORMATION SHEET D) ETHICAL COMMITTEE APPROVAL ORDER E) PLAGIARISM	

Introduction

Systemic lupus erythematosus (SLE) is the prototype autoimmune disease with varied clinical manifestations due to involvement of a variety of organ systems simultaneously or serially over a period of time. Similar to other rheumatic diseases the disease activity has to be controlled and maintained in a state of remission or low activity. Hence we have to monitor the disease activity periodically and adjust the dosage of medications.[1]

The disease can be either in a state of remission or can be chronically active or can be of remitting and relapsing type with intermittent flares. For measuring the disease activity, we do a clinical assessment followed by laboratory investigations. Some of the immunological investigations like anti ds DNA and complements are still not affordable by everybody in a country like ours. The very purpose of this study is to look for other alternatives which can indirectly gauge the disease activity during a flare.

In SLE, cardiovascular system is equally affected like any other system. Even though the incidence of overt manifestations might be less common compared to other organs, at autopsy the incidence was found to be more.[2]Among the various causes of death in SLE, it is the third common cause. QT interval parameters have been found to point towards increased risk of death due to a cardiovascular cause and also helps in assessing the prognosis clinically.[2] The purpose of this study is to identify whether QT interval calculation helps to assess the disease activity indirectly at baseline and during flares and hence indirectly the prognosis and cardiovascular risk.

Among the QT interval parameters we have corrected QT interval (QTc) which when prolonged has been found to cause ventricular tachyarrythmias and sudden cardiac death. Similarly QT dispersion (QTd) which is the variability of QT interval from lead to lead in a single person has been found to be related with unstable electrical activity and arrhythmias of ventricles.[3] By calculating the QT interval parameters we can find out the risk of cardiac death, its correlation with disease activity and its use as a surrogate marker. The conduction system involvement can also be the cause for these cardiac events. Anti Ro & La antibodies have been found to have relation in neonates with various cardiac manifestations but no strong association has been found in adults.[4] We also wanted to find its correlation with QT interval parameters and the disease activity.

During our daily management we found that Erythrocyte Sedimentation Rate (ESR) has been found to increase with disease activity. But it has remained controversial. Hence we wanted to confirm it in our study as it could be the cheapest and readily available surrogate marker ever. Similarly serum uric acid levels were also higher in SLE patients at diagnosis irrespective of renal failure and its correlation with disease activity is also part of the study. Cutaneous involvement is one of the commonest manifestations in SLE. Most of our patients have cutaneous manifestations at presentation and also worsening during flares. Whether cutaneous activity indirectly indicates the overall severity of autoimmunity and hence the disease activity in SLE patients is a thought provoking issue. Though there are various activity indices for skin we used the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) in this study. Simlarly many disease activity indices are there to calculate the same in SLE but in this study we use SLEDAI which is simple to use clinically and has been tested in various clinical trials.

Aim

To study the correlation between QTc interval parameters and disease activity in patients with SLE

Primary objectives :

1. To study the correlation between QT interval parameters (QTc interval & QT dispersion) and disease activity in patients with SLE.

2. To study QT interval parameters during episodes of flare (on follow up).

Secondary objectives :

1. To study the correlation between QT interval parameters & auto antibodies.

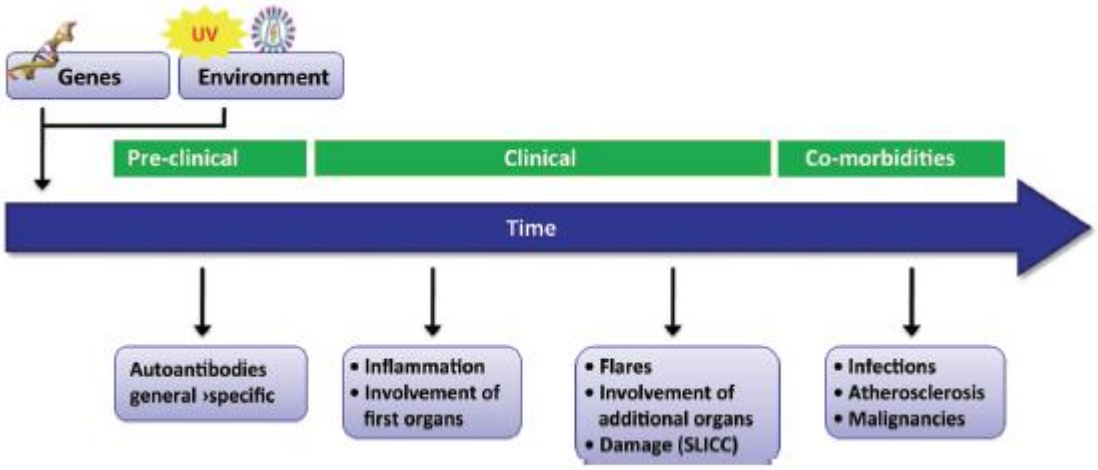
2. To study the correlation between ESR and disease activity (SLEDAI).

3. To study the correlation between serum uric acid and disease activity (SLEDAI).

4. To find out the correlation between CLASI and disease activity (SLEDAI) in patients with cutaneous manifestations of SLE.

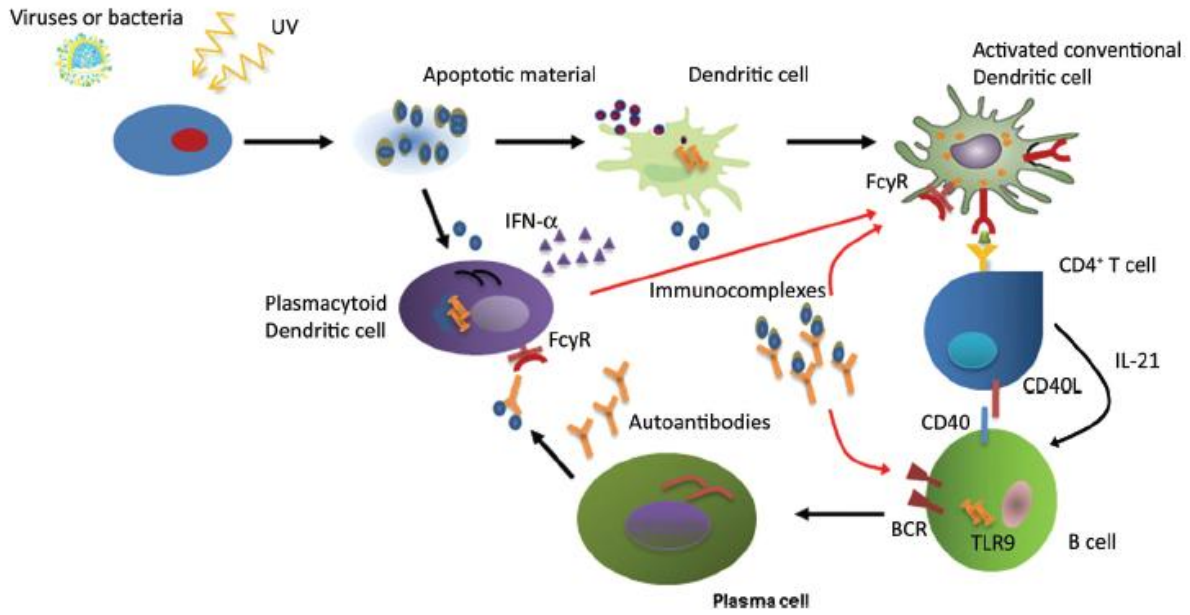
Review of literature

SLE is the typical autoimmune disease with varied manifestations involving all organ systems. The disease activity in SLE is a chronic ongoing one with intermittent relapses and remissions. If the disease activity is not controlled early it will lead on to organ damage with chronic morbidity or mortality if severe. Like other autoimmune diseases no single etiology exists and needs multiple factors for development of the disease. There is interaction between both environmental and genetic factors which might be single or multiple. The natural history of disease is depicted in the diagram below.[5]



Pathogenesis: The main mechanism in SLE is mounting of immune response against self nuclear antigens. Initially there is a nonspecific viral infection or some other environmental agent causing cell injury and apoptosis. The apoptotic material is presented by antigen presenting cells (mainly dendritic cells) to T cells. The B cells are activated in turn by these T cells. The cytokines and cell surface molecules involved are IL-10, 23 and CD 40L, CTLA-4. Other than this T cell dependent mechanism there exists a T cell independent one where B cell receptor & Toll like

receptor aids in activation of B cells. Below is a diagrammatic representation of the pathogenesis in SLE.[5]



Cardiovascular System (CVS) and Lupus:

The classic manifestations of SLE like cutaneous, renal etc. are being managed better now and hence CVS manifestations has become one of the major causes for morbidity and mortality. SLE with high disease activity, dosage of steroid used and disease duration are the factors definitely contributing to increased cardiovascular events and dysfunction of endothelium subclinically.[7-10] The main cytokine which favours atherogenesis and dysfunction of endothelium in lupus patients are Type I interferons.[11] Neutrophil Extracellular Traps (NETs) formation leads to extrusion of chromatin and granular material outside the cell and might be the initial step of atherogenesis and also in causing dysfunction of the endothelium.[1] The various cardiac manifestations are Pericarditis (the most common) with or without pericardial effusion, myocarditis, endocarditis, coronary vascular disease & conduction system abnormalities.

Myocarditis is seen clinically in only 10% of patients but seen in 50% on autopsy studies.[12] When a SLE patient presents with conduction defects, arrhythmias, unexplained cardiomegaly or tachycardia, then myocarditis has to be suspected. Since myocardial involvement may not be overt it has to be detected with ECG (74% abnormality), ECHO (72% abnormality) or CXR (55 % abnormality). Newer modalities like Thallium scan, Cardiac MRI, SPECT can also identify abnormalities. There are also studies showing association of anti Ro and anti La auto antibodies with myocarditis.[13-16] Other than these manifestations there can be dysfunction of autonomic nervous system which is more common in older women who attained menopause & those with peripheral nerve disease, systemic hypertension & cerebrovascular accident. They can also have atrioventricular blocks & less variation of periodic heart rate.[17,18]

In general sudden cardiac death secondary to rhythm and conduction disturbances are more in autoimmune rheumatic diseases. The reason for arrhythmias are due to re entry and due to altering or triggering of automaticity. In SLE the major cause for sinoatrial or atrioventricular node dysfunction is due to vasculitis of small vessels and granular or fibrous infiltration of nodes.[19] In 34-70% of patients conduction abnormalities can be secondary to myocarditis.[20] Usually they have a transient first degree heart block and rarely complete heart block (associated with anti U1RNP antibodies rather than anti Ro antibodies).[21]In contrast, conduction defects with myocarditis is more correlated with anti Ro antibodies and they are reversible on controlling the disease.

In a study done by Josiane Bourre Tessier et al the QT interval prolongation was associated with the presence of anti Ro antibodies.[4] In another study done by Logar D et al they found that conduction abnormalities and

myocarditis were more common in SLE and had an association with anti Ro antibodies.[14]

In a prospective study carried out by Moacir Fernandes de Godoy et al "patients with confirmed diagnosis were analyzed over a period of 13 years and concluded that there is cardiac impairment which keeps progressing and some even needed interventional procedures like angioplasty and emphasized the need for a meticulous cardiac follow up on a long term basis in patients with lupus".[22]

QT interval :

Measurement of QT interval is important as both increase or decrease in QT beyond normal variation leads to sudden arrhythmias and acute cardiac death. As per Ilan Goldenberg et al. we have various computerised methods to assess QT interval like "individual-based corrections for repolarization duration, quantitative assessment of repolarization morphology, correction for repolarization dynamicity and analysis of repolarization variability." But in this study we have used the manual determination method otherwise called as eyeball method or caliper method. Other than this it can be calculated manually by digitizing or on screen calculation in a computer.[23]

The automatic methods are not accurate most of the time and should be followed by a manual reading. But the best method is to record the ECG and display it on the screen of a computer or to scan the recorder ECG and then measure it on the screen with computer based calipers. It is the ideal method recommended as it provides ECG with high quality.

Usually the speed at which ECG is recorded is 25 millimeter per second with an amplitude of 10 millimeter per mill volt. With manual measurement, the level of accuracy of calculation is 20 to 40 milliseconds. The QT interval value is calculated as a mean of three to five cardiac cycles and measured from where QRS complex starts to where T wave ends. Measurement of QT interval is made in lead II & V5/V6 and the value which is longest is chosen.[23]

How to overcome the practical difficulties in measuring QT interval?

The difficulty is to correctly identify the T wave with its descending limb intersecting the isoelectric line and when U waves are nearby the T wave. We then identify the descending limb of T wave intersecting with TP baseline (provided there is no U wave succeeding the T wave or when both waves can be identified separately). When the T wave is biphasic we usually take the point of final return of the T wave. QRS interval can be altered sometimes due to conduction blocks or drugs. The accurate duration of repolarization can't be measured and the JT interval has to be measured. The 'S wave off point' to end of T wave is measured as JT.[24]

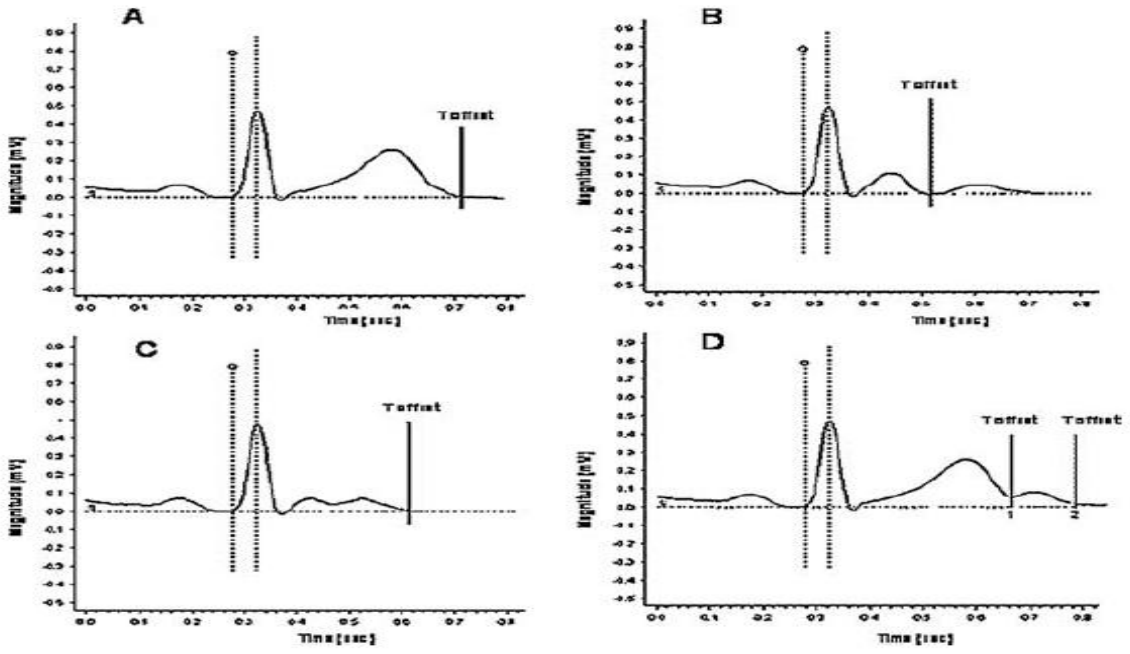


Figure A: Normal T wave morphology

Figure B: Presence of U wave

Figure C: Presence of biphasic T wave

Figure D: Presence of T2 wave (another repolarization wave with a low amplitude)

How to adjust for heart rate?

All the ECG intervals vary with the heart rate i.e R-R interval. We have to correct for the heart rate to calculate the duration of repolarization. We have various methods or formulae to correct for the QT interval with reference to a predicted value (calculated with a 60 per minute heart rate).All these formulae have been obtained from ECGs in resting state and need a normal sinus rhythm with no sudden fluctuations. By correlating between the QTc intervals obtained with a formula and the RR intervals we can assess the way in which a formula has performed. The correction formulae are not really successful unless we get a value which doesn't differ from zero and most of the formulae used actually don't. Here in the table below we have the various formulae used for calculation.[24]

Method	Formula	Comment
Exponential		
Bazett	$QTc = QT/RR^{1/2}$	Widely used; may give erroneous results at both slow and fast heart rates
Fridericia	$QTc = QT/RR^{1/3}$	Widely used; may give more consistent results at fast heart rates
Linear		
Framingham	$QTc = QT + 0.154(1\text{-}RR)$	May have more uniform rate correction over a wide range of heart rates
Hodges	$QTc = QT + 1.75(HR\text{-}60)$	
Rautaharju		May have more uniform rate correction over a wide range of heart rates
Females and males <15 and >50 years	$QTI = (QT[HR + 100])/656$	
Males 15–50 years	$QTI = 100(QT)/([656/(1 + 0.01HR]) + 0.4–25)$	
Logarithmic		
Ashman	$QT = K1 \times \log(10 \times [RR + K2])$	At low heart rates, the values are too low
Adult men	$K2 = 0.07$, and $K1 = 0.380$	
Adult women	$K2 = 0.07$, and $K1 = 0.390$	

The most common formula used clinically is the Bazett's formula. The corrected QT interval is calculated by dividing the QT interval (in seconds) by the RR interval

(in seconds) preceding it. With a faster heart rate it may overcorrect and it may under correct with a slower heart rate. For an ECG with fast heart rate the Fridericia formula corrects accurately. From the Framingham study the linear formula was derived. No uniform opinion is available on the formula which can be used in clinical practice. But with heart range in normal limits (60-90/min) most of the formulae give similar results.[23]

How to calculate for ECGs with sinus arrhythmias ?

We need advanced methods to evaluate repolarization dynamics in ECGs with no stable heart rate. QT hysteresis/Lag is the adaptation of QT interval to heart rate changes with a delay. The adaptation of QT interval to accelerations is faster than decelerations. Hysteresis is the QT versus RR interval plot representing the dynamic changes with respect to the heart rate and forms a loop. It is a highly individualized pattern.[23]

What are the normal values of QT interval?

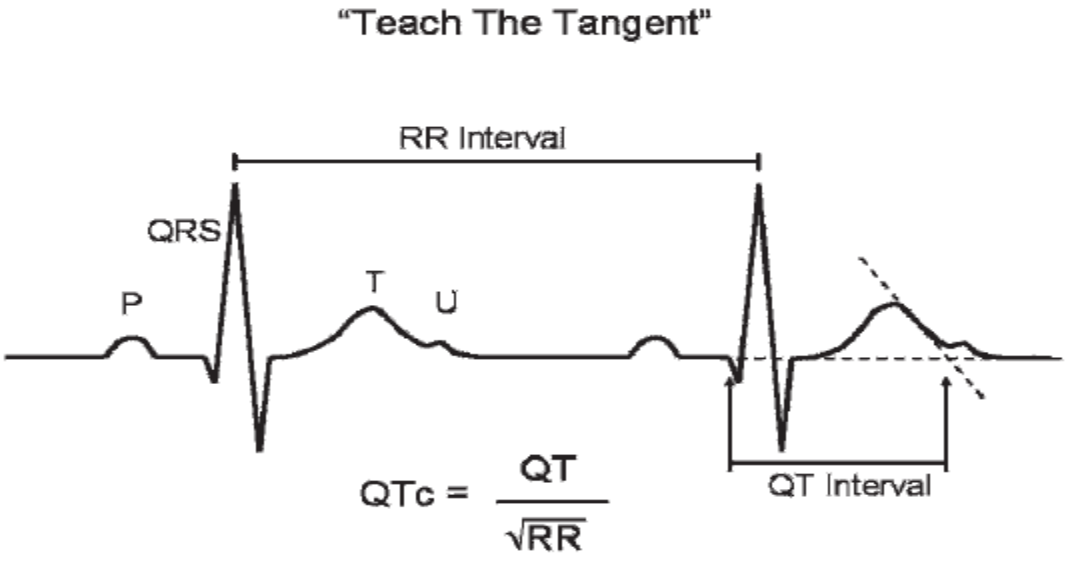
As discussed above, the Bazett's formula is used most often and all the reference values for QT intervals are based on that formula. Based on a study done in 581 healthy subjects (included adult males, adult females and children) a set of values have been described to detect QTc prolongation and is mentioned in the table below.[25]

Rating	1–15 years (msec)	Adult Male (msec)	Adult Female (msec)
Normal	<440	<430	<450
Borderline	440–460	430–450	450–470
Prolonged	>460	>450	>470

How repolarization morphology helps in calculation ?

By using measurements like T wave symmetry, area under T wave and interval from where T wave ends to peak of T wave (maximum amplitude) we can quantify repolarization. But it needs a specific software on computer and the ECG data has to be stored electronically. By visually assessing the T wave and its repolarization pattern we can can place it under the specific software category for assessment. For example, in patients with different types of long QT genotypes different patterns of T waves were observed.[26] In type I usually we have a T wave which is broad based, single, uniform and at times T waves with late onset but normal morphology are also seen. In type II T waves with bifid morphology are seen. In type III, T waves are peaked, prominent and has a late onset.[26]

"Teach the tangent" method: It is otherwise called as 'avoid the tail method'. It is used mainly for ECGs with atypical T waves. The method was tested on a group of 151 medical graduates and they achieved a diagnostic accuracy of 77% which was far better than the accuracy of cardiologists and non cardiologists using normal methods.[27, 28]



Other methods like Holter monitoring and exercise testing can also be used to assess ventricular repolarization but these methods have not been standardized for primary assessment of ventricular repolarization. For events which occur very rarely in a day the Holter monitoring is of immense use but data obtained from an ECG and Holter can't be compared directly. For exercise tests a standard protocol is followed to assess the QT interval during periods of exercise and recovery.

On long term following up of patients over years when ECG is repeated for an individual the QT interval differs substantially. So for abnormal values it is better to take multiple ECGs rather than a single ECG.[23-26]

In a study by Viskin S et al, "calculation of QT intervals manually was correct 96% of times when done by QT experts, 62% by arrhythmia experts and only less than 25% by cardiologists and others." But still, simple methods of assessing QT interval in routine ECGs helps us to assess the ventricular repolarization, provided we have a criteria which uniformly assesses the offset of T wave, heart rate correction and morphology of T wave.[27-30]

QT dispersion(QTd):

As we discussed above, the QTc measurement was considered to reflect the repolarization of ventricles. Later it was found that the QT interval varied between different leads. So the difference between maximum and minimum QT interval was calculated and named as QT dispersion. It was found to be a fine marker of increased ventricular vulnerability to arrythmias.[31-33]

Initially the concept of QT dispersion was quite reasonable and many a time the association between arrhythmias and ventricular recovery time was

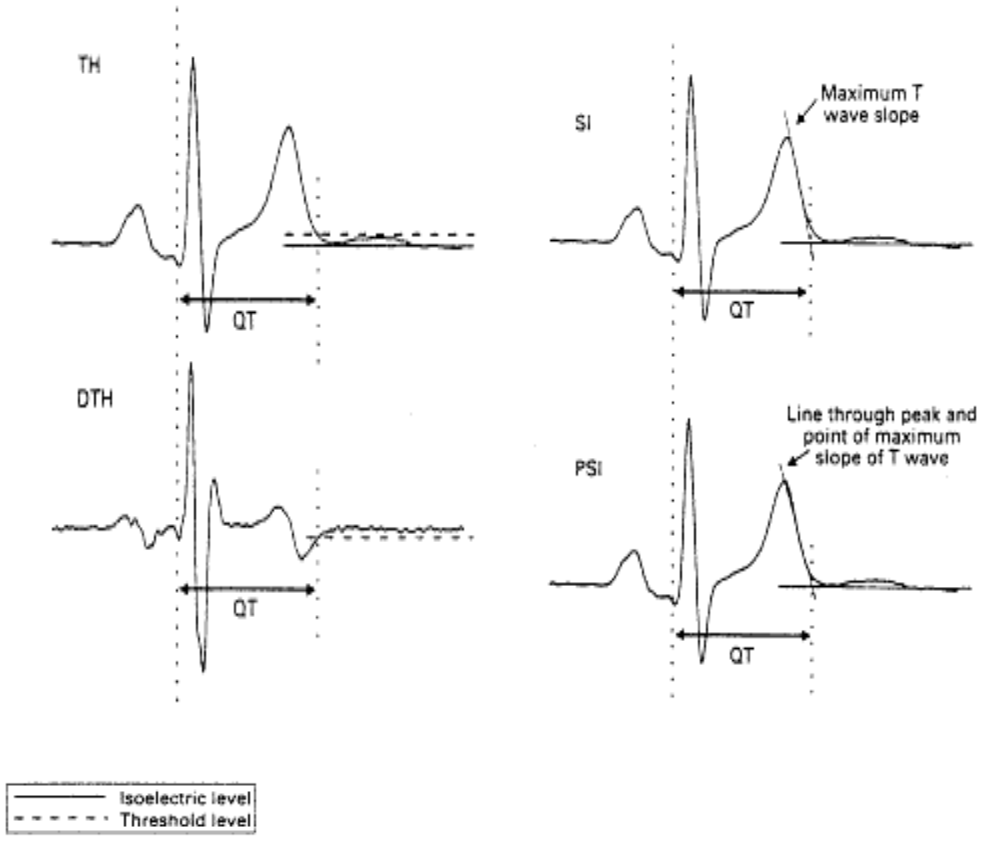
proved.[29,34,35] It was thought that ventricular recovery time and its dispersion was reflected by QTd. A high degree of correlation was established between intracardiac monophasic action potentials and the QTd parameters. The ventricular recovery time heterogeneity is reflected by QTd and a value in the range of 70-120 ms can predict the increased risk for arrhythmias.

As discussed above, both manual and computer based methods are prone for errors. The main cause is the T wave morphology, its amplitude (if low) and when it merges with a U or P wave. Various methods used to measure are:

1. Threshold method.

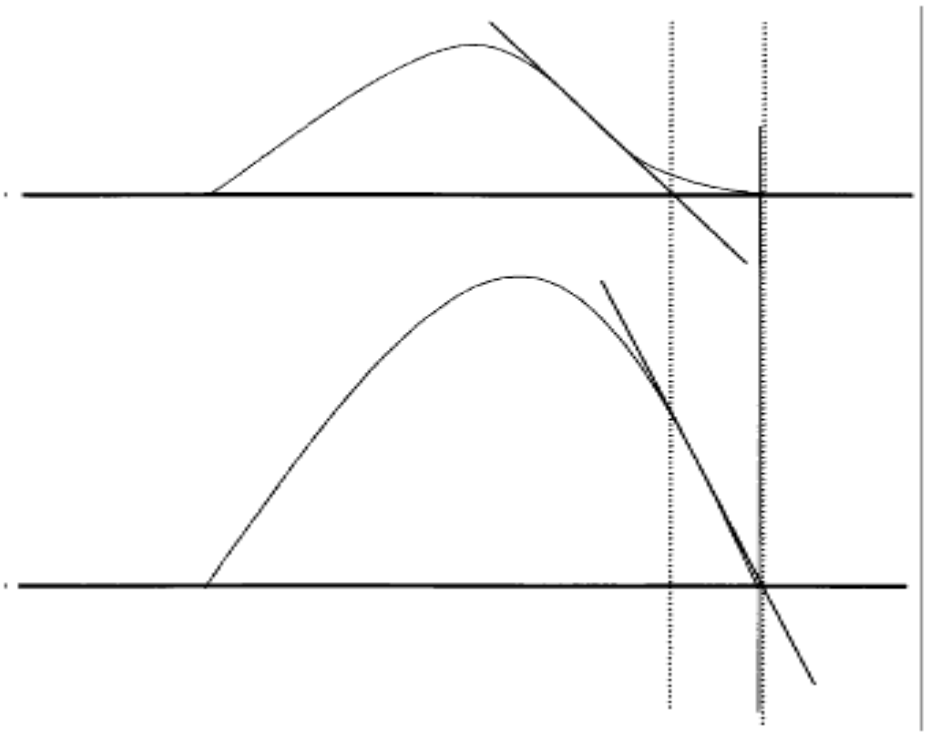
2. Slope method.

3. Tangent method.



Below in the first two figures,"to the original T wave (TH) or to its differential (DTH) the threshold method has been applied. In the slope method, a tangential line is drawn to the steepest point (SI) of descending arm of T wave. In the tangent method a line is drawn through (peak of) T wave and the maximum slope point (PSI)." [36]

For exact measurement of QTd, we have to simultaneously record all the 12 ECG leads so that there is no effect of heart rate on dynamicity of QT and it is considered the gold standard. The corrected QT dispersion has been used in many large scale studies. Additive & multiplicative formulae are used for heart rate correction. Although there is evidence for influence of rate, rhythm and site of impulse origin on ventricular recovery times it doesn't hold good for QT dispersion.[36]



But ultimately it depends on the shape of descending limb of T wave and its amplitude.[36] Both T waves have the same offset (2nd dashed vertical line) but descending waves are of different shapes. So in the first T wave there is underestimation and in second there is overestimation as per "teach the tangent method"

In a study done by A.Cindas et al, QT dispersion was calculated in rheumatoid arthritis patients. "It was found that RA patients had more of diastolic dysfunction and heterogeneity of repolarization. Patients with disease duration of more than 5 years had significant longer values of QTd."[37]

In another study, done in 38 patients with systemic sclerosis by Sgreccia.A et al, QTc interval and QT dispersion was significantly prolonged in systemic sclerosis patients when compared with controls.[38]

Özhan Göldeli et al assessed QT and JT dispersion in patients with Behcet's disease and it was found to be increased significantly indicating regional variation in repolarization and the possible reason for ventricular arrhythmias.[39]

In an Iranian study done by Javad Kojuri et al, 124 SLE patients were studied. Two groups were formed, one with high disease activity (SLEDAI>10) and another with low disease activity (SLEDAI<10). QT dispersion was studied in them and it was found to have a significant correlation in the group with high disease activity. In patients with active disease, to assess the cardiac risk it can be used noninvasively as a simple tool.[2]

Assessment of disease activity: SLE is an autoimmune disease involving multiple systems and is heterogenous in nature. Since the disease activity fluctuates widely it

is not possible to assess disease activity with a single tool.[40] The five domains[41] with which a patient with SLE is assessed are:

- Disease activity
- Damage
- HAQoL
- Adverse events
- Economic costs & impact

In this study and also in our routine clinical practice, we use tools to assess disease activity which is an ongoing continuous process and is reversible. But disease damage is a permanent sequelae due to disease and is not reversible. In terms of disease activity usually three patterns are observed.[40-42] They are:

- Disease flare
- Chronically active disease
- Quiescence

We have various modalities to assess disease activity like clinical assessment and laboratory investigations (hematology, urine examination, immunological tests etc.). All these will be incorporated into the various disease activity assessment indices. Two types of disease activity measurement indices are there:

Global disease activity indices (overall burden of disease): The disease activity and its recent changes are assessed. Disease activity can be quantified and is of immense use in clinical practice. No consideration is given for individual organs. Disease with multiple minor manifestations scores the same as few major organ manifestations. Many of the indices don't

differentiate the change in activity (improvement or worsening) over the past month.[43]

Organ specific indices (activity in individual organ systems): Ideal tool for disease activity assessment in a heterogenous disease like SLE.

The five commonly used disease activity assessment tools are:

1. British Lupus Isles Assessment Group Index (BILAG)

2. Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)

3. Systemic Lupus Activity Measure (SLAM)

4. The Lupus Activity Index (LAI)

5. The European Consensus Lupus Activity Measurement Index (ECLAM)

BILAG:

It was first published in 1988. The index was initially based on eight organ systems, with manifestations occurring in the past 28 days.”Intent to treat” is the principle on which it is based. The ratings used are:

Action (9): severe disease which needs a steroid dosage of – prednisone > 20mg/day + other immunosuppressant’s or anticoagulants ,added if necessary

Beware (3): disease is less active and needs low dose steroids, antimalarials, NSAID’S

Contentment (1): disease is mild and stable, needs no modification of therapy

Discount (0): system not affected now but affected in past

E (0): system has never been affected

It is scored from 0 – 4 with 4 = new or recurrent; 3 = worsening; 2 = same; 1 = improving; 0 = absent. The systems included are general features, mucocutaneous, musculoskeletal, neurological, cardio respiratory, renal, haematological, ophthalmic, gastrointestinal and hepatic.

Later the index was modified in 2004. In the new index the number of organ systems were increased to nine with inclusion of ophthalmologic, gastrointestinal & hepatic manifestations. The vasculitis category was taken off and its components were redistributed into the respective organ systems. Also some components like avascular necrosis were removed as it was more indicative of damage. Another important aspect is, there was no place for immunologic abnormalities in this system. To automatically calculate the A-E scores a computerised program called BLIPS (British Lupus Integrated Prospective System) is available. Even though it was initially studied in adult lupus it was also validated for childhood lupus in 2004.[41-44]

SLEDAI:

In 1985 there was introduction of SLEDAI, a global disease activity index. It is more objective, more convenient and commonly used in clinical practice. It has 24 parameters based on nine organ systems and has a total score of 105 and the manifestations should be present in the previous ten days.[45,46] It includes immunologic parameters and is more reliable and valid in both adult and childhood lupus. It also predicts the 6 month mortality rate (as mentioned in the table below).[47]

SLEDAI	RELATIVE RISK
1-5	1.28
6-10	2.34
11-19	4.74
>20	14.11

Modifications of SLEDAI:

MEX – SLEDAI :

This was the MEXICAN version where the immunologic parameters were removed due to increased cost involved in calculating.[48]New features like mononeuritis multiplex, myelitis, fatigue were included with grouping of peritonitis with serositis, elevated creatinine with renal system, lymphopenia and hemolysis with haematological system. Features like pyuria, lupus headache and visual disturbances were omitted. The number of variables were decreased to ten and total score to only 32. It was originally validated in only Spanish speaking countries and not widely used in trials.[48]

SELENA-SLEDAI:

In the Safety of Estrogen in Lupus Erythematosus National Assessment Trial (SELENA) the SLEDAI was again modified. To improve the clarity, some of the definitions were modified. Seizures secondary to previous CNS damage and CVA secondary to hypertensive causes were excluded. New features like scleritis, episcleritis and vertigo were added. Proteinuria was modified by adding "new onset or recent increase in proteinuria to the existing definition of proteinuria more than 500mg/day".[49]

SLEDAI – 2K:

In 2002 it was introduced and also validated. The change here was, certain parameters like oral ulcers, rashes, alopecia and proteinuria were included by their mere presence and not necessarily new or recurrent ones. Like SLEDAI it is also a predictor of mortality. Then came the 30 day version of SLEDAI 2K. Like many other indices here also disease activity was assessed over the past 30 days. The explanation for the change was that, any manifestation present from 11^{th} to 30^{th} day can't resolve completely in the 10 days before a clinical visit.[50]

SLAM :

It is another index which assesses the global disease activity and was introduced in 1989. It has 31 items (23 clinical + 7 laboratory) encompassing 11 systems with a score of 86. The score ranges from 0-3. Later SLAM was revised with omission of immunologic parameters. Compared to other indices, subjective items are more in SLAM and hence patient's assessment is captured better.[51]

ECLAM:

In 1992 it was first introduced with a total of 15 manifestations (9 clinical + 3 laboratory) with individual scores from 0.5-2 and a total score of only 10. Again the manifestatios present over previous 30 days are taken for assessment. It is best suited for retrospective studies and also validated for childhood lupus. But it is not often used in clinical trials.[52]

LAI : It is divided into 5 parts with scoring from 0-3 and the manifestations scored, have to occur in the past 14 days.[46] They are :

- PGA : Physician's global assessment

- Arthritis, serositis, rash, fatigue
- Renal , neurological, pulmonary and haematological
- Steroids and cytotoxic agents in high doses
- Urinary sediments, anti ds DNA, C3, C4 levels

Scoring is by calculating mean of part one score added to mean of 4 items of part two plus maximum score of part three plus mean of score in part four and five.

Lupus Foundation of America (LFA) formed a working group to define disease flare in lupus. They defined disease flare as *"any increase in disease activity which can be measured and occurrence of a new manifestation or worsening of a manifestation in any organ system. It is a temporary measure which has to be considered clinically significant by the examiner and necessitating a change in treatment."*[44]

Disease activity is due to signs, symptoms or laboratory abnormalities present at the time of evaluation without any reference to previous activity and flare is with reference to previous activity.[44]

Based on various indices flare can be defined. They are :

1.SLEDAI: Increase by 3 – Flare

Decrease by 3 – Improvement

Within 3 Points – Persistent Disease

Score of 0 - Remission

2.BILAG:

New category A – Severe Flare

Two, new category B manifestations – Moderate flare [53]

3. SELENA SLEDAI FLARE INDEX (SFI):[54,55]

It has 3 components.

Mild flare is defined as:

a. SELENA SLEDAI score >3

b. New or worsening disease activity (Fever, Arthritis, Serositis, Mucocutaneous lesions), change in medications (predisone <0.5 mg/kg/day) and addition of HCQ/NSAID's

c. Physician's global assessment (VAS: increase by 1.0-2.5)

Severe flare is defined as:

a. SELENA SLEDAI score > 12
b. New or worsening of neuropsychiatric SLE, lupus nephritis, vasculitis, myositis.

   Platelet counts<60 000, hemolytic anemia with Hb<7% or decrease in Hb by 3%

   Doubling of dosage of steroids / prednisolone>0.5 mg/kg/day or need for hospitalization

   Addition of cyclophosphamide, azathioprine, methotrexate etc.
c. Increase in PGA > 2.5

Improvement is assessed by:

RIFLE (Responder Index For Lupus Eryhtematosus): It is used in clinical trials to measure complete and partial responses. It can assess the change in disease activity over time. The response obtained is absent, complete resolution, incomplete response, unchanged or worsening of manifestations. It needs further validation and is not approved in childhood SLE.[56]

SLE Responder Index: It was first developed and used in a class II trial of Belimumab in SLE. Modified SLEDAI, SELENA-SLEDAI, BILAG and PGA have been incorporated in it to detect a change in disease activity. SELENA-SLEDAI was used to assess global disease activity, BILAG for individual systems and PGA was used so that importance is given also for patient's individual assessment.[57]

SLEDAI 2K Responder Index 50(SRI-50):

It covers the same 9 systems and 24 variables present in SLEDAI 2K and score ranges from 0-105. To recognize a clinically meaningful improvement the clinician should document at least a 50% improvement in an individual variable.[58]

Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI):

SLE has a wide variety of skin lesions categorized into acute, sub acute and chronic. But among the various manifestations, cutaneous lesions have never been studied systematically. The main reason is lack of a validated disease activity index to assess the effect of treatment. For developing a good cutaneous disease assessment index in SLE many had tried but very few exist. Few of them like Dermatology Index of Disease Severity (DIDS) exists but are quite rough, in their estimation of body surface area for diseases like SLE.[59]

Separate scores for activity and damage: As present in other disease assessment scores of SLE, for skin also separate scores for activity and damage was proposed. The rationale is, a patient with scarring will have a stable score but clinically has no disease activity and only damage. The treatment for a scarred lesion is totally different from one with active disease but with the same score.[59] It is scored separately for

1. Cutaneous lesions
2. Mucous membrane and
3. Alopecia

For cutaneous involvement both activity and damage are scored. Areas scored are Scalp, Ears, Nose + Malar area, Rest of face, V area of neck, Posterior neck , Chest, Abdomen, Back + Buttocks , Arms, Hands, Legs and Feet – 13 areas in total.

For cutaneous activity two aspects are scored:

1. Erythema (score of 0-3)
2. Scale / Hypertrophy (score of 0-2)

For damage two aspects are scored:

1. Dyspigmentation (score of 0-1)
2. Scarring/Atrophy/Panniculitis(score of 0-2)

For mucous lesions active lesions or ulcerations indicate activity and dyspigmentation indicates damage.

For alopecia scalp is divided into four quadrants with nonscarring alopecia indicating activity and scarring alopecia indicating damage.

So the combined total score for cutaneous, mucous membranes and alopecia is scored separately for activity and damage.

It has a total score of 70 and three grades of severity: [60]

1. Mild disease : 0-9
2. Moderate disease : 10-20
3. Severe disease : 21-70

There is a separate scoring for associated symptoms like pain, itching and fatigue on a visual analog scale of 0-10. It was also found to have good content and face validity and also performed well for inter rater and intra rater validity. The extent of disease is assessed here by number of anatomical areas (those which are exposed given more importance than those which are covered by clothes) involved rather than the percentage of surface area involved, which have been used in other scores(eg. PASI). Erythema is the main parameter on which activity score is based and it is easy to recognize erythema even in dark skinned individuals. The average time required for scoring is five minutes[59]

In a study done by Salphale P et al. the CLASI score was applied to 93 patients of SLE with cutaneous lesions. The mean CLASI activity score was 15.4 and mean damage score was 6.87. Patients who had a combination of lesions had higher activity scores and damage scores positively correlated with the disease duration. Thus the effectiveness of CLASI for cutaneous disease assessment was shown in this study.[61]

CLASI was not validated initially in studies conducted by rheumatologists for disease activity and damage assessment. Jolly. M et al did a study on a group of 31 patients with cutaneous SLE and used CLASI to assess the cutaneous activity and damage and found that it correlated well with the physician disease assessment for both activity and damage.[62]

A study done by Yokogawa N et al. conducted a trial on use of HCQ in cutaneous lupus and found that CLASI was a reliable tool to assess the treatment response to HCQ.[63]

In another study done by Bein.et al CLASI was used to assess the various types of skin lesions in cutaneous lupus. They found that it is quite useful to assess overall disease activity and damage but not quite accurate to assess some of the individual subtypes and hence recommended a revision.[64]

Erythrocyte sedimentation rate:

ESR is one of the oldest markers for inflammation still being used widely as it is cheap and easily done. Unlike other acute phase reactants (whose concentration increases or decreases by more than 25% from baseline), it is an indirect measure of acute phase response. The change actually taking place is an increase in serum fibrinogen level plus other factors which influence ESR. ESR is the rate at which RBCs settle down when blood is kept in a vertical tube. The surface charge and frictional forces of RBCs play a major role in determining the rate of erythrocyte sedimentation. To increase the rate of settling, the negative charge on RBCs (zeta potential) has to be decreased. The decrease in zeta potential is brought by an increase in asymmetrical proteins like fibrinogen and to some extent by $alpha_2$, beta and gamma globulins. Other than these factors, even alteration in properties of RBCs

can influence ESR. Decrease in albumin or increase in cholesterol may increase ESR. Certain non inflammatory conditions (pregnancy, diabetes), malignancies, infections, chronic renal failure, monoclonal gammopathy and even drugs can influence ESR.[65-69]

As per the International committee for standardization in Hematology the recommended method for ESR estimation is Westegren method. The recommended upper limit value for males is 15mm/hr and for females is 20mm/hr. It also varies with age, race and sex.[68,69] One of the formulas used for ESR estimation in males and females are :

MALES = AGE/2

FEMALES = AGE+10/2

G. Stojan et al found that disease activity as measured by SELENA-SLEDAI had significant correlation with ESR. It also correlated well with renal, haematological, arthritis, serositis, rash and Physician's global assessment (PGA).[69]

In a survey of 570 SLE patients 56% of the patients had elevated ESR.[70] Since it correlates well with disease activity it has found a place in the Systemic Lupus Activity Measure (SLAM).[71] But the utility of ESR in monitoring disease activity is not certain as the studies available have been not consistent due to confounding factors and other coexisting conditions.[69]

As per the LUMINA study "553 SLE patients were studied in a total of 2317 visits. ESR was divided into four categories: normal (0-25mm/hr), mild (25-50mm/hr), moderate (50-75mm/hr) and severe increase (>75mm/hr). It was shown that mild, moderate and severe elevation in ESR had a strong correlation with disease activity

in SLE. Moderate and severe elevation also correlated better with extent of damage. Hence it was concluded that ESR is an easier and cheaper way of assessing disease activity and damage.[72] But the limitation of the study was that the coexisting conditions were not studied properly."

In an Iranian study done by Nasiri et al, 100 patients with SLE were studied and found a significant association between BILAG scores and ESR.[73]On the contrary, in another study done by Mirzayan et al there was no correlation between ESR and disease activity. Similarly Chang et al showed no association between ESR and SLAM-R/SLEDAI. But patients with low ESR felt that their condition improved."[74]

In a study of HLA DR4 by T cells by Viallard et al 60 patients with SLE were studied and divided into high and low disease activity groups. They found that the high disease activity group had a quite high ESR.[75]

In another study done by Samsonov MY et al. where ECLAM was being compared with neopterin, beta2 microglobulin, p55 TNF receptor, soluble IL 2 receptor and soluble CD8 they found that ESR had a strong correlation with ECLAM.[76] In a Brazilian study where the association between disease activity and terminal complement complex (sC5b-9) was studied it was found that ESR was raised in those with moderate and severe disease activity.[77]

URIC ACID AND SLE:

In our study we found that many of our SLE patients had elevated serum uric acid. On searching the literature there was no study correlating the disease activity and levels of serum uric acid in SLE. Hence in our study we wanted to study the same. In one of the German studies uric acid levels was assessed in patients with various

rheumatic disorders. A total of 1715 patients were studied and 79 of them had SLE. They found that average serum uric acid levels were higher in patients with SLE.[78]

In another study done by Frocht A et al 38 patients with SLE were studied. 29% of them had increased uric acid levels. It was found to have an association with renal involvement and in particular diuretic therapy and proteinuria. They also concluded that when uric acid levels are high with joint symptoms, gout has to be thought of rather than SLE arthritis, as symptoms due to gout may be suppressed by anti inflammatory medications.[79]

In a study done by Ho HH.et al 15 SLE patients were studied and two of them had overlap features. All these patients were under excretors and 14 of them were on diuretics. Many of them also had comorbidities like hypertension and cardiovascular problems. It was also found that gouty attacks occurred when SLE was inactive.[80]

Yang Z et al did a study to find an association between serum uric acid and lupus nephritis in patients with SLE. 130 SLE patients were studied and 73 of them had lupus nephritis. It was found that for development of lupus nephritis, uric acid was an independent risk factor. They also found a negative correlation between uric acid and complement(C3) levels in patients with lupus nephritis.[81]

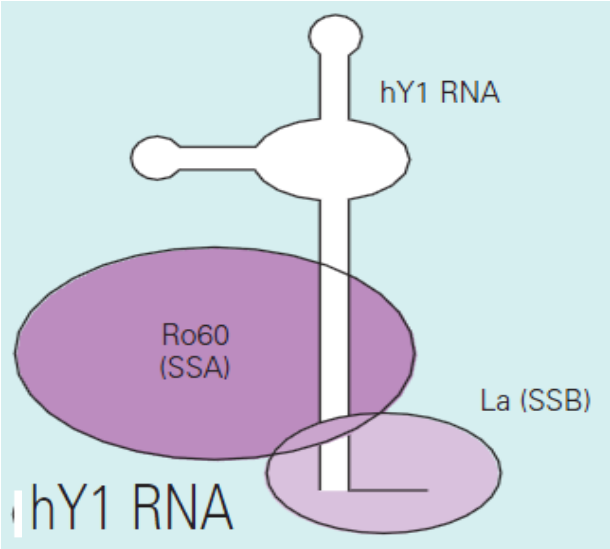
In another study done by Kim KJ et al, 114 patients with SLE were studied and 7.9% of them had pulmonary hypertension and these patients also had high disease activity. It was found that serum uric acid levels were significantly elevated in patients with pulmonary hypertension and at levels more than 6.5 mg/dl it was predictive for the same with reasonable accuracy. It also correlated with pulmonary artery systolic pressure and NT-pro BNP levels. It was concluded that uric acid

levels can act as a surrogate marker for predicting development of pulmonary hypertension in SLE.[82]

In another study by Yang Z et al 191 SLE patients were studied and association between serum urea, creatinine and uric acid levels and clinical and laboratory parameters independent of renal involvement were studied. Serum uric acid level had a positive association with erythrocytopenia.[83]

In a study done by JM Sabio et al, a group of 102 SLE patients without obvious cardiovascular diseases secondary to atherosclerosis were studied. The main aim was to find any correlation between serum uric acid levels and arterial stiffness and inflammation markers. "They observed that patients with increased uric acid levels had a poor cardiovascular risk profile (inclusive of ageing, obesity, hypertension, raised cholesterol levels, metabolic syndrome and renal disease). They also found that SLE duration was more with increased accrual of damage. It was concluded that in SLE patients without obvious atherosclerotic cardiovascular disease, uric acid levels may be an ancillary indicator of subclinical atherosclerosis."[84]

Anti Ro and Anti La antibodies:



A group of cytoplasmic ribonucleoproteins containing the 60-kDa Ro antigen and one of the Y1, Y3, Y4 or Y5 RNA molecules are recognized by Anti Ro autoantibodies. A donut like structure is formed by Ro 60 antigen through which ssRNA passes. The 47-kDa La antigen is transiently associated with precursors of many small RNAs being synthesized by RNA polymerase III and to protect them from the activity of exonucleases. Hence for RNA polymerase III, the termination factor is La antigen. Ro 60 also attaches to RNAs which are misfolded and helps in quality control of U2 and 5S ribosomal RNA. UV radiation promotes misfolding of RNA and anti Ro confers protection by promoting degradation of the same. Though Ro 52 is not an integral part of Y1-Y5 RNP particles, anti Ro 52 antibodies usually coexist with anti Ro 6o and La auto antibodies.

The diseases with which anti Ro and La auto antibodies associated are Sjogren's syndrome, SLE, PM/DM and SSc. The prevalence rates of anti Ro 60 autoantibodies are 60-80% in primary Sjogren's syndrome and 10-50% in SLE. The anti La antibodies have a prevalence of 10-20% in both Sjogren's and SLE and it always coexists with anti Ro 60 and/or La. All three antibodies also predispose to neonatal cardiac abnormalities like congenital complete heart block. Pregnant patients with previous history of conduction defects in fetus or patients with SLE should be screened for the presence of these auto antibodies as it increases the fetal risk during pregnancy. Usually it is the IgG antibodies which crosses the placenta and binds the autoantigens present on apoptotic cells. The inflammatory response and fibrosis with production of TNF is mediated by Fc receptors. The second trimester (particularly 22^{nd} - 30^{th} weeks) is the period with increased risk and needs fetal cardiac monitoring. Dexamethasone or plasmapheresis has a role in treatment of low grade heart block.[85-88]

The manifestations associated with anti Ro in SLE patients are photosensitivity, cutaneous lupus, chilblains, sicca symptoms, congenital heart block, anti La, Rheumatoid factor, C4 deficiency, pulmonary disease, endocardial fibroelastosis, lymphopenia and thrombocytopenia. Anti La is associated with late onset SLE, secondary Sjogren's and also protection from nephritis due to anti Ro.[89-91]

Materials and methodology

The study was done on newly detected SLE patients admitted in the Department of Rheumatology, Madras Medical College & RGGGH, Chennai .

Duration of study: January 2012 – December 2013

Design of the study: Prospective analytical study

Ethical committee approval: Obtained before starting the study.

Consent: Informed consent in patients own language was obtained

Study group: 100 consecutive SLE patients and 100 age matched controls attending the Department of Rheumatology, RGGGH, Chennai who satisfied the inclusion criteria were studied.

Inclusion Criteria:

- Patients who satisfied the 1997 revised ACR classification criteria for SLE with a normal good quality resting ECG were included in the study group.
- Patients who attended master health check up and other outpatients who had non rheumatological disorders.

Exclusion Criteria:

- Patients with electrolyte disturbances.
- Drugs prolonging QT interval (except chloroquine).
- Patients with baseline ECG abnormalities (eg: bundle branch blocks , presence of U waves).

- Pre-existing cardiac disease (eg: ischemic heart disease, congestive heart failure, rhythm abnormalities)

- Renal failure

Methodology:

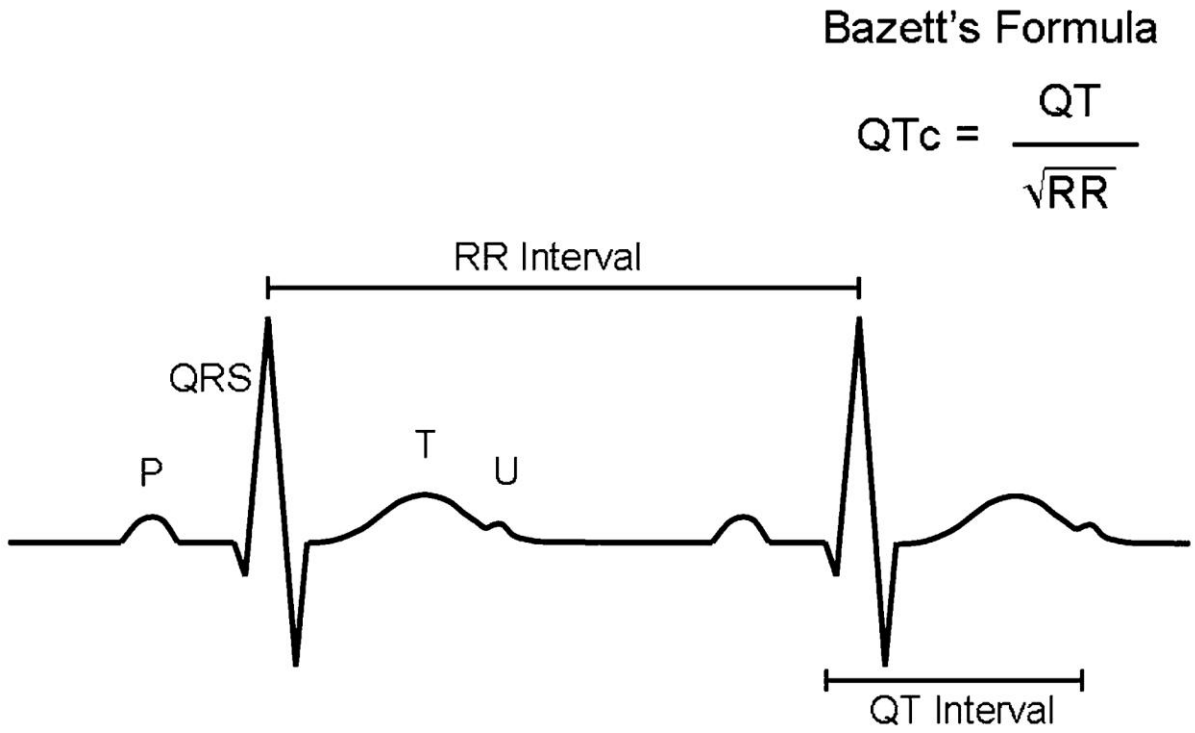
All patients who satisfied the inclusion criteria were chosen and detailed history was obtained and complete clinical examination was done. Patients were subjected to baseline blood investigations and immunological investigations. ESR was calculated with Westergren's method & serum uric acid (determined by Trinder's method) with automated analyser. ANA was done by either ELISA or IIF by Hep-2 method, anti dsDNA by ELISA & complements by nephelometry. ANA profile 3 was done by EUROIMMUNE Line Immunoassay (Immunoblot).

A standard 12 lead Electrocardiogram was obtained with a speed of 25mm/sec & 10mm/mV amplitude. QT interval was calculated from beginning of 'q' wave to end of T wave in lead II or lateral leads (V5,V6). QT dispersion was measured as the difference between maximum & minimum QT intervals. Trans thoracic Echocardiogram was done by a cardiologist.

Patient's generalized disease activity was calculated with SLEDAI (Annexure A2) and CLASI (Annexure A3) was used to assess the activity and damage due to skin lesions. The same disease activity measurement tools were used during each flare on follow up and necessary blood investigations (baseline & immunological), urine routine and repeat ECG were also obtained.

QT interval calculation: In the diagram below we can see two consecutive cardiac cycles with measurement of QT interval from where QRS starts to where T wave

ends. The typical U wave is also seen but it should be excluded from the calculation. Then the interval between two cardiac cycles (i.e RR interval) should be calculated. Then the Bazett's formula was used to calculate the corrected QT interval.



Statistical analysis:

For discrete data proportion are computed and the mean and standard deviation are computed for the continuous data. The Chi square test was applied to compare the proportions between the groups. The independent t test was used to compare the mean between the groups. All analyses were two tailed and $p<0.05$ was considered significant. Pearson's correlation coefficient was used to measure the linear correlation between two variables. SPSS version 21.0 was used for data analysis.

ANA ELISA

Principle:

In the ANA screen ELISA kit, purified nuclear antigens are being coated on to wells of microtitre plate. If IgG type of ANA specific antibody is present it binds to the antigen. Washing is done to remove all the unbound materials. If any antigen antibody complex is there, it binds to the added enzyme conjugate. Again washing is done to remove excess enzyme conjugate and then substrate is added. On incubation of the plate there is hydrolysis of the substrate by the enzyme.

Test procedure:

- Universal precautions are followed during the procedure. All the reagents are dispensed in the centre of the well and the tip of the pipette should not touch the wall of the micro well.
- Prepare work sheet and remove the kit from the refrigerator and leave it at room temperature for 30 minutes.

Sample:

- Use only serum as specimen for the test

Preparation of wash buffer:

- Check the buffer concentrates for the presence of salt crystsls.
  50ml of buffer is prepared for each strip
- Mix 20ml 25x wash buffer concentrate with 480 ml of distilled water

Procedure:

- Samples to be brought to room temperature
- Samples arranged so that well A1 is negative control and well B1 is positive control and well C1 & D1 is calibrator.
- To 200 µl of sample diluents, 10 µl of test sample is added to make a 1:21 dilution and mixed nicely.
- Dispense 100 V of diluted sera in E1 well & other diluted samples in their appropriate wells. Tap the holder to remove air bubbles from the liquid and mix well gently and cover with a seal.
- At room temperature incubation is done for 20 minutes
- The seal is removed and wash buffer of 300 µl is used to wash the wells thrice.
- An absorbent paper is used for blotting.
- In each well enzyme conjugate of 100 µl is added.
- The plate is sealed with a cover and is incubated for 20 minutes at room temperature.
- The seal is removed and wash buffer of 300 µl is used to wash the wells thrice.
- An absorbent paper is used for blotting.
- Dispense 100 µl of TMB substrate and incubate for 10 minutes at room temperature.
- Add 100 µl of stop solution.
- Read at 450 nm using ELISA reader

ANA – INDIRECT IMMUNOFLUORESCENCE (Hep-2)

Principle:

The antibodies present in the sample bind the relevant antigens. Once bound, the antigen-antibody complex is shown with an antibody conjugated with fluorescein and is visualized under a fluorescent microscope.

Test procedure:

- Keep the slides at room temperature for 30 minutes before performing the assay.
- The phosphate buffer saline is prepared before performing the assay.
- According to the slide to be used, prepare a screening dilution.

Reagents	1/10 dilution	1/40 dilution
PBS buffer	450 µl	300 µl
Serum	50 µl	100 µl

- With diluted samples and diluted controls the reactive areas are covered.
- Incubation is done at room temperature for a period of 30 minutes. Perform a quick wash with PBS.
- Three washings should be performed of 5 minutes each, putting the slides in the coplin jar containing PBS, shaking softly.
- Take the slides off the PBS, shake the excess on absorbent paper and keep the reactive areas wet.

- Diluted Anti IgG FITC is used to cover the reactive areas immediately and kept for incubation at room temperature in a moist chamber for 30 minutes.
- Steps for washing to be repeated.
- Cover the reactive areas with Evan's blue.
- Wash the excess stain with PBS, keeping the reactive areas wet.
- Put the mounting medium immediately on the cover slide.
- Results are interpreted based on the pattern and the intensity of fluorescence in 1/40 dilution. Positive reaction in 1/10 dilution but negative in 1/40 dilution is reported as negative.

ANA profile 3

Procedure:

To take the strip provided by the manufacturer and place it on the tray.

To add 10 µl serum sample to 100 µl diluents (30 minutes Incubation)

Thrice washed with 1.5 ml wash buffer (incubate for 5min / wash)

Add 100 µl conjugate (30 minutes Incubation**)**

Thrice washed with 1.5 ml wash buffer (incubate for 5 min / wash)

Add 100 µl substrate (10 minutes Incubation)

Wash with 1.5 ml distilled water

Add 100 µl stop solution (5 minutes Incubation)

Read results

Results and Analysis

Table 1: Age wise distribution of study cases

Age (years)	Males	Females	Total
17- 20	2	22	24
21-25	6	31	37
26-30	5	17	22
31-35	1	7	8
36-40	-	5	5
41-45	-	2	2
46-50	-	1	1
51-55	-	1	1

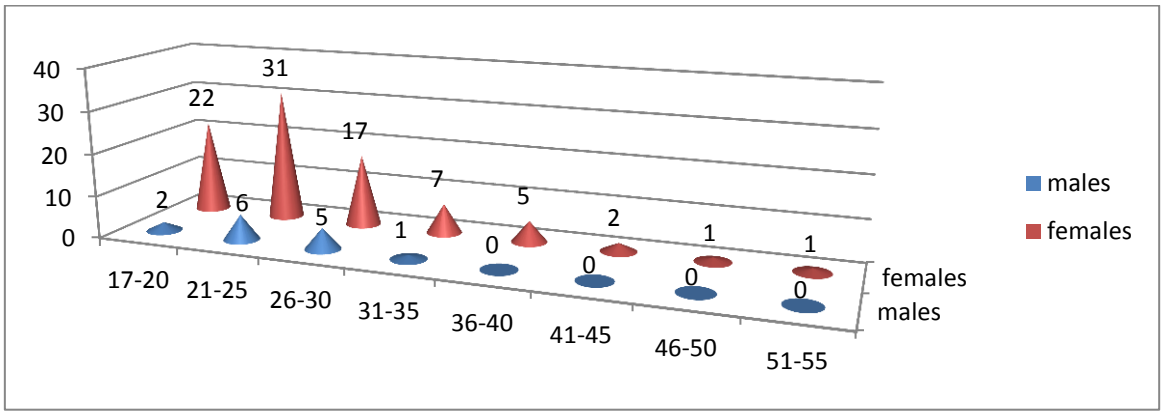


Figure 1 Age Distribution

The study group had 59% of the patients (48% - females & 11% - males) in the age group of 21-30 years. There were 24% (22% - females & 2% males) of patients in age group of 17-20 years. The maximum number of patients were from 2nd and 3rd decades.

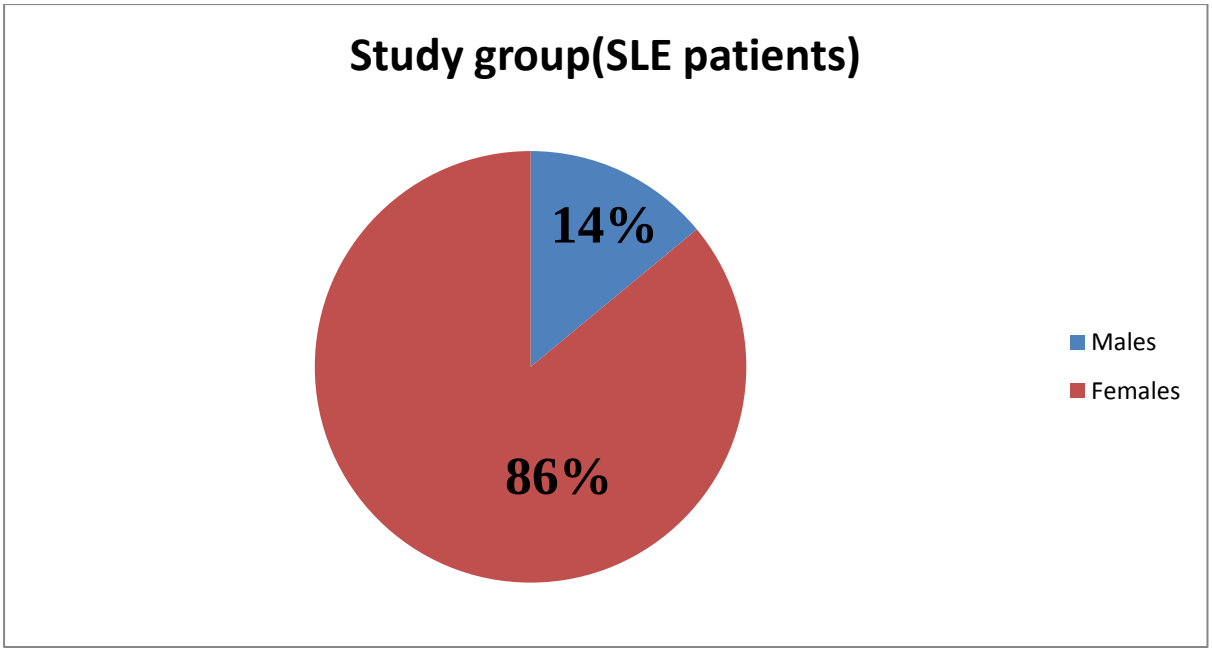


Figure 2 : Gender Distribution

Table 2: Sex distribution in cases and controls

	Males	Females	Total
Cases	14	86	100
Controls	25	75	100

Among the cases 86% were females and 14% were males. Among the controls 75% were females and 25% were males.

Table 3: Clinical features

Type of manifestation	No: of subjects (%) (n=100)
Fever	81
Arthritis	61
Cutaneous	58
Neuropsychiatry	45
Renal	44
Hematological	43
Myositis	41
Hepatomegaly/Splenomegaly	39
Lymphadenopathy	33
Serositis	32
Cardiovascular	29
Pulmonary	11
Weight loss	11

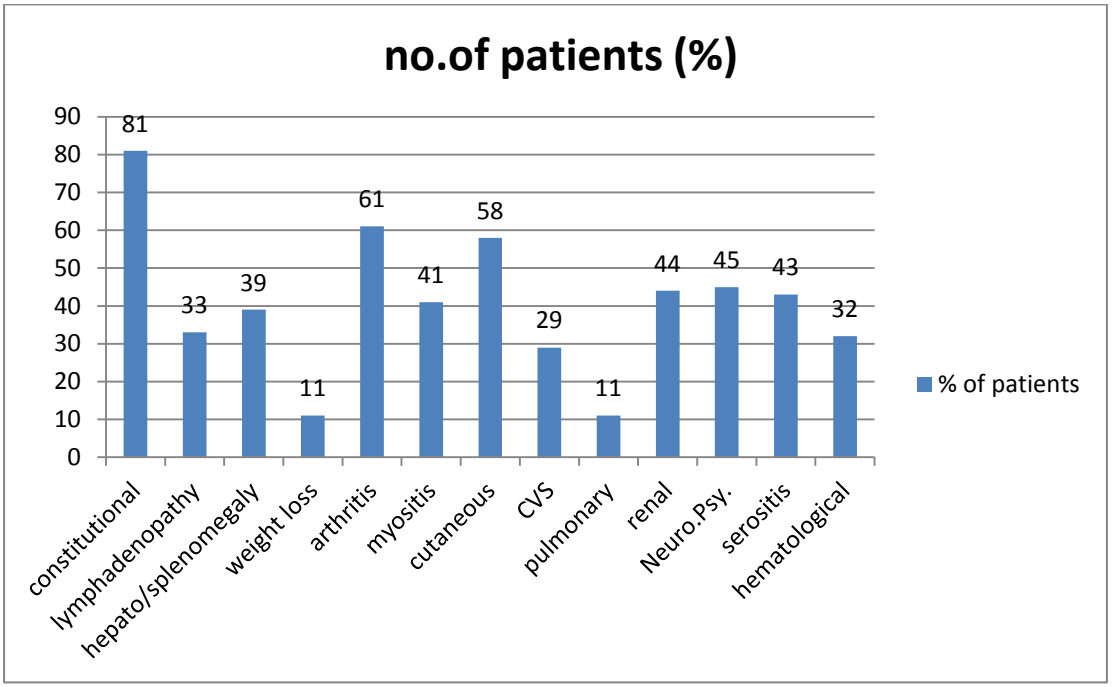


Figure 3 Clinical Features

In our study group 61% had arthritis ,58% had cutaneous,45% had neuropsychiatry, 44% had renal involvement, 43% had serositis, 32% had haematological , 29% had CVS involvement and 41% had myositis.

Table 4: Lupus nephritis (ISRN/RPS 2003)

Class	No: patients	%
I	2	4.54
II	3	6.81
III	10	22.72
IV	17	38.63
V	7	15.9
VI	1	2.27
III + V	1	2.27
IV + V	2	4.54
V + VI	1	2.27

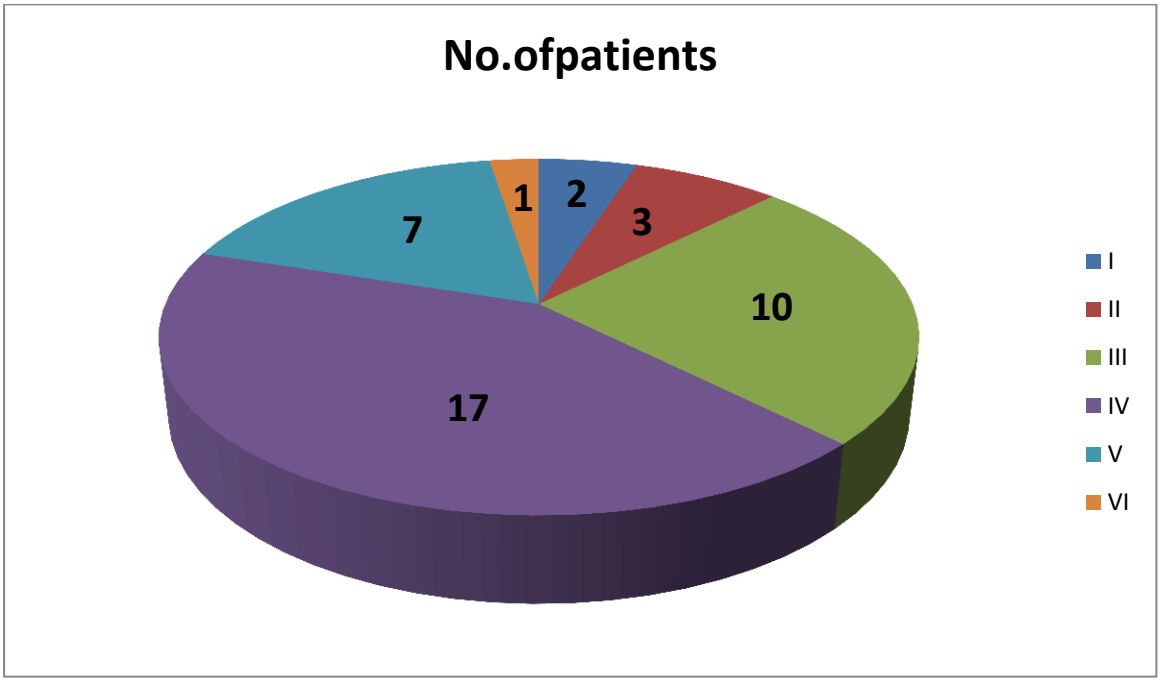


Figure 4 Lupus nephritis

In our study group class IV lupus nephritis was common (38.63%), followed by class III (22.72%) and class V (15.9%).

Table 5: Frequency of Auto antibodies

Auto antibodies	No. of Patients (%)
anti Sm	49
anti Ro	47
anti ds DNA	45
anti U1 RNP	42
anti Histone	31
anti Ribosomal P protein	28
anti Nucleosome	28
anti La	10

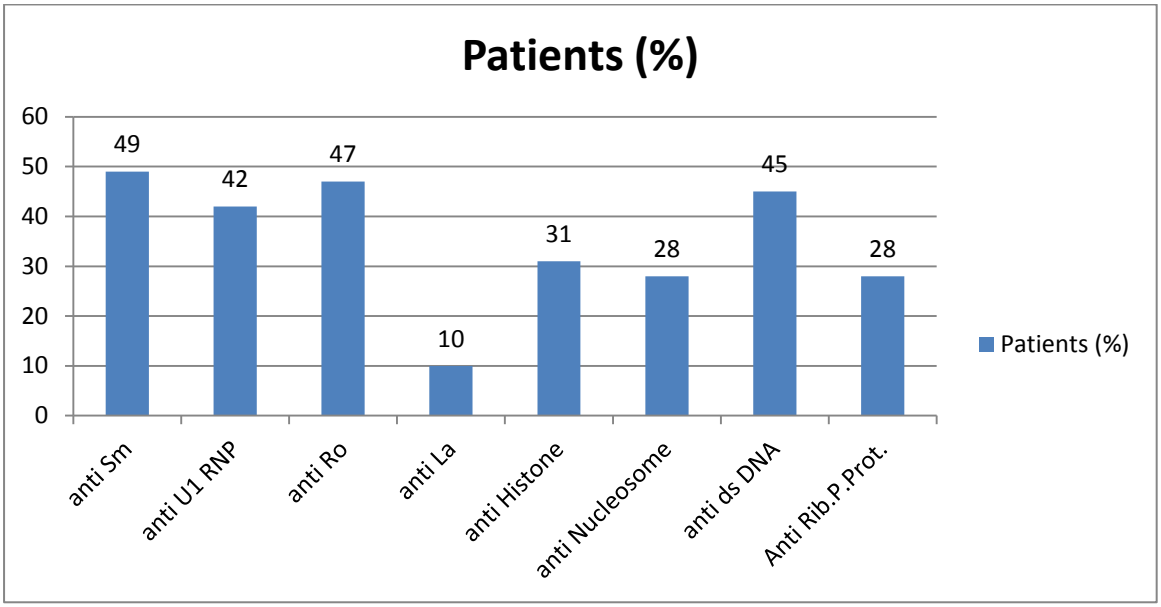


Figure 5 - Auto antibodies (%)

Anti Sm was found in 49%, followed by Anti Ro (47%), Anti ds DNA (45%) and Anti U1RNP(42%).

Table 6: SLEDAI distribution

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	UP TO 5	1	1.0	1.0	1.0
	6-10	15	15.0	15.0	16.0
	11-15	21	21.0	21.0	37.0
	16-20	17	17.0	17.0	54.0
	21-25	22	22.0	22.0	76.0
	26-30	9	9.0	9.0	85.0
	31-35	6	6.0	6.0	91.0
	36-40	5	5.0	5.0	96.0
	41-45	4	4.0	4.0	100.0
	Total	100	100.0	100.0	

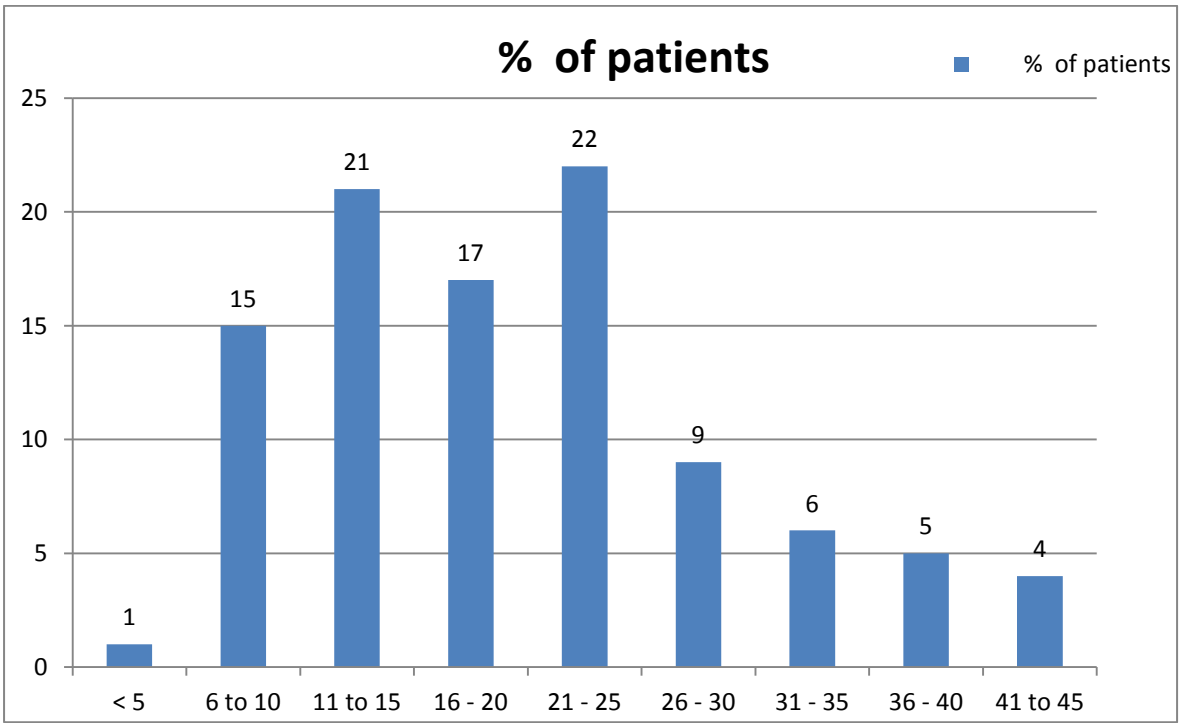


Figure 6 SLEDAI

84% of the patients in our study had high disease activity.

Table 7: Disease Flare

	Frequency	Percent	Valid Percent	Cumulative Percent
	75	75.0	75.0	75.0
mild	7	7.0	7.0	82.0
moderate	9	9.0	9.0	91.0
severe	9	9.0	9.0	100.0
Total	100	100.0	100.0	

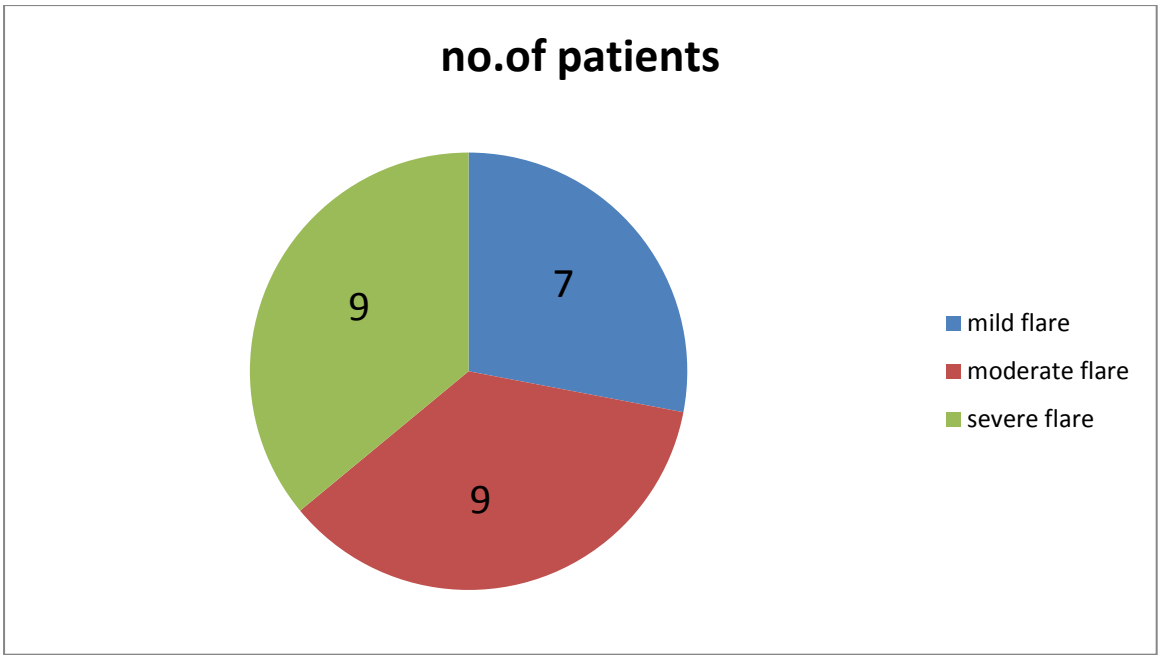


Figure 7 patients with flare

In our study group of 100 patients, 25 patients had flare, of which 28% had mild flare, 36% had moderate flare and 36% had severe flare.

Table 8: ESR* distribution

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	UP TO 25	4	4.0	4.0	4.0
	26-50	41	41.0	41.0	45.0
	51-75	41	41.0	41.0	86.0
	76-100	14	14.0	14.0	100.0
	Total	100	100.0	100.0	

*correction for anemia : corrected Hb = (ESR X Hematocrit/45)

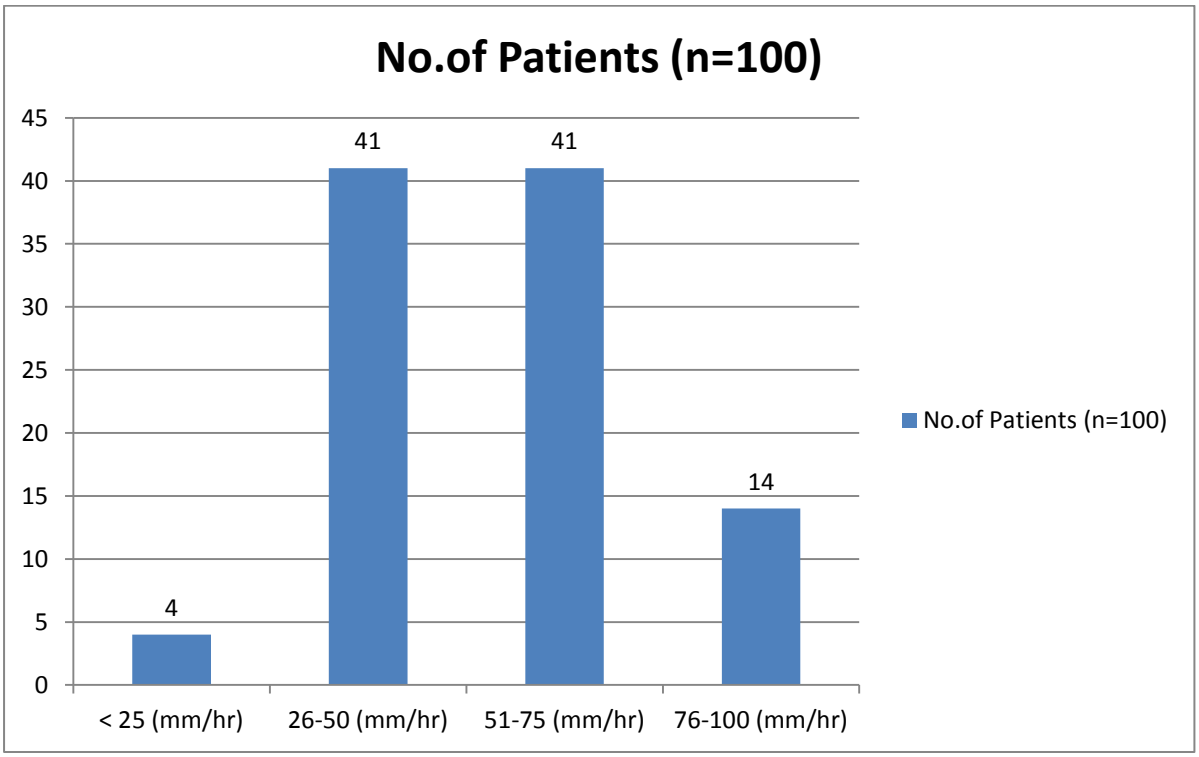


Figure 8 - ESR distribution

In our study group, 4% had ESR less than 25 mm/hr, 41% had between 26-50 mm/hr, 41% between 51-75 mm/hr and 14% had ESR between 76-100 mm/hr.

Table 9a: Acute cutaneous lupus

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	NO	58	58.0	58.0	58.0
	YES	**42**	**42.0**	42.0	100.0
	Total	100	100.0	100.0	

Table 9b: Subacute cutaneous lupus

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	NO	74	74.0	74.0	74.0
	YES	**26**	**26.0**	26.0	100.0
	Total	100	100.0	100.0	

Table 9c: Chronic cutaneous lupus

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	NO	87	87.0	87.0	87.0
	YES	**13**	**13.0**	13.0	100.0
	Total	100	100.0	100.0	

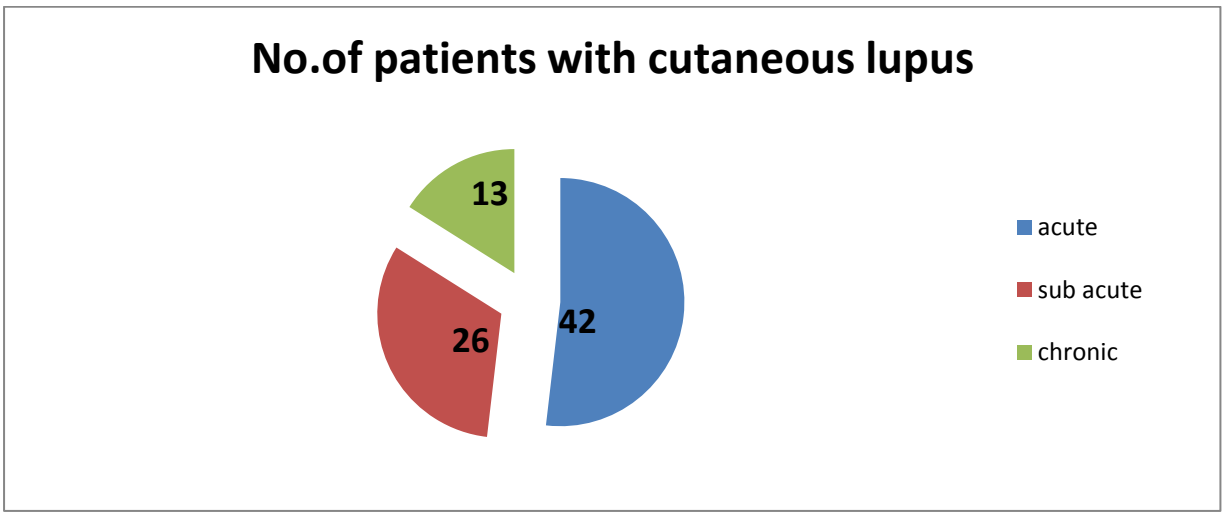


Figure 9 - Cutaneous Lupus Types

In our study group 42 had acute cutaneous lesions, 26 had sub acute cutaneous lesions and 13 had chronic cutaneous lesions.

To find if there is any difference in the mean QTc between cases and controls

Group Statistics(t test)

	GROUP	N	Mean	Std. Deviation	Std. Error Mean
Corrected QT interval	Cases	100	436.30	27.433	2.743
	Controls	100	397.24	31.853	3.185
QT dispersion	Cases	100	44.40	20.613	2.061
	Controls	100	39.20	17.734	1.773

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed) **P value**	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
Corrected QT interval	Equal variances assumed	4.407	.037	9.292	198	**.000**	39.060	4.204	30.770	47.350
	Equal variances not assumed			9.292	193.740	**.000**	39.060	4.204	30.769	47.351
QT dispersion	Equal variances assumed	4.809	.029	1.912	198	.057	5.200	2.719	-.162	10.562
	Equal variances not assumed			1.912	193.683	.057	5.200	2.719	-.163	10.563

Inference: QTc difference between cases and controls is statistically significant as p<0.0001 and the QTd difference is not significant between the cases and controls.

To find out the correlation between baseline QTc interval and QTc interval during flare

Variables:

QTcb1=QTc value at the beginning for **mild** flare cases corresponding to QTcf1 value.

QTcb2=QTc value at the beginning for **moderate** flare cases corresponding to QTcf2 value

QTcb3=QTc value at the beginning for **severe** flare cases corresponding to QTcf3 value

Test of relationship between QTc values for flare cases with baseline QTc values is seen by

Pearson's correlation coefficient.

Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	QTcb1 & QTcf1	7	.433	.331
Pair 2	QTdb1 & QTdf1	7	.559	.192
Pair 3	QTcb2 & QTcf2	9	.560	.117
Pair 4	QTdb2 & QTdf2	9	.280	.466
Pair 5	QTcb3 & QTcf3	9	.863	**.003**
Pair 6	QTdb3 & QTdf3	9	.614	.079

Inference:

QTc baseline and QTc during a flare have a positive correlation and similarly QTd baseline and QTd during flare also have a positive correlation.

But only the difference between **severe (flare) associated QTc values and baseline QTc values are statistically significant.**

To find out the difference between the mean QTc (baseline) and mean QTc (flare) and mean QTd (baseline) and mean QTd (flare).

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed) **P value**
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	QTcb1 - QTcf1	5.429	24.144	9.126	-16.901	27.758	.595	6	.574
Pair 2	QTdb1 - QTdf1	20.000	25.820	9.759	-3.879	43.879	2.049	6	.086
Pair 3	QTcb2 - QTcf2	-6.333	18.480	6.160	-20.538	7.871	-1.028	8	.334
Pair 4	QTdb2 - QTdf2	.000	20.000	6.667	-15.373	15.373	.000	8	1.000
Pair 5	QTcb3 - QTcf3	-6.667	8.456	2.819	-13.166	-.167	-2.365	8	**.046**
Pair 6	QTdb3 - QTdf3	-4.444	16.667	5.556	-17.256	8.367	-.800	8	.447

Inference:

QTc difference for cases with severe flare is statistically significant.

For cases with mild and moderate flare the difference is not significant for QTc as well for QTd.

Mean QTc interval and QTd of anti Ro (+ ve) vs anti Ro (- ve) patients

Group Statistics

	Anti Ro Antibody	N	Mean	Std. Deviation	Std. Error Mean
Corrected QT interval(cases)	Positive	47	448.87	17.926	2.615
	Negative	53	425.15	29.648	4.072
QT dispersion (cases)	Positive	47	44.26	20.825	3.038
	Negative	53	44.53	20.622	2.833

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed) **P value**	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
Corrected QT interval(cases)	Equal variances assumed	15.057	.000	4.765	98	**.000**	23.721	4.978	13.843	33.600
	Equal variances not assumed			4.902	86.997	**.000**	23.721	4.840	14.102	33.341
QT dispersion (cases)	Equal variances assumed	.014	.907	-.066	98	.948	-.273	4.151	-8.510	7.964
	Equal variances not assumed			-.066	96.341	.948	-.273	4.153	-8.517	7.971

Inference:

The mean QTc difference between anti Ro positive and anti Ro negative cases are statistically significant.

The mean QTd difference is not significant for Anti Ro positive and negative cases.

Mean QTc interval and QTd of anti La (+ ve) vs anti La (- ve) patients

Group Statistics

	Anti La Antibody	N	Mean	Std. Deviation	Std. Error Mean
Corrected QT interval(cases)	Positive	10	445.90	21.236	6.716
	Negative	90	435.23	27.929	2.944
QT dispersion (cases)	Positive	10	40.00	13.333	4.216
	Negative	90	44.89	21.266	2.242

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed) **P value**	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
Corrected QT interval(cases)	Equal variances assumed	1.273	.262	1.169	98	.245	10.667	9.128	-7.447	28.780
	Equal variances not assumed			1.455	12.744	.170	10.667	7.333	-5.207	26.540
QT dispersion (cases)	Equal variances assumed	6.849	.010	-.710	98	.480	-4.889	6.888	-18.558	8.781
	Equal variances not assumed			-1.024	14.688	.322	-4.889	4.775	-15.086	5.308

Inference:

The mean QTc difference and the mean QTd difference between anti La positive and negative cases are not statistically significant.

Table 10: CLASI activity and damage scores of Acute, Subacute and Chronic cutaneous lesions

	No. of patients	Mean	Std.Deviation	Std.Error Mean
Acute CLASI activity	42	8.88	7.235	1.116
Acute CLASI damage	42	3.00	4.596	.709
Subacute CLASI activity	26	13.54	8.296	1.627
Subacute CLASI damage	26	5.54	4.329	.849
Chronic CLASI activity	13	10.23	8.228	2.282
Chronic CLASI damage	13	8.23	5.805	1.610

Table 11: Correlation between SLEDAI and corrected QT interval (QTc) in cases

Correlations

		SLEDAI	Corrected QT interval(cases)
SLEDAI	Pearson Correlation	1	.331**
	Sig. (2-tailed)		**.001**
	N	100	100
Corrected QT interval(cases)	Pearson Correlation	.331**	1
	Sig. (2-tailed)	.001	
	N	100	100

**. Correlation is significant at the 0.01 level (2-tailed).

Inference:

The Pearson Correlation coefficient 'r'=0.331 between the *SLEDAI and QTc is statistically significant as p = .001.*

Hence we conclude that there is *significant correlation between SLEDAI and QTc interval.*

Table 12: Correlation between SLEDAI and QTdispersion (QTd) in cases

Correlations

		SLEDAI	QT dispersion (cases)
SLEDAI	Pearson Correlation	1	-.048
	Sig. (2-tailed)		.632
	N	100	100
QT dispersion (cases)	Pearson Correlation	-.048	1
	Sig. (2-tailed)	.632	
	N	100	100

Inference:

The Pearson Correlation coefficient 'r'=-0.048 between the SLEDAI and QTd is not statistically significant as p=0.632 >0.05

Hence we conclude that there is no correlation between SLEDAI and QTd.

Table 13: To find out correlation between between the QTc(cases) and the CLASI

Correlations

		Corrected QT interval(cases)	CLASI
Corrected QT interval(cases)	Pearson Correlation	1	.101
	Sig. (2-tailed)		.321
	N	100	99
CLASI	Pearson Correlation	.101	1
	Sig. (2-tailed)	.321	
	N	99	99

Inference:

As ‘r’=0.101 and p=0.321, the relationship between the QTc and CLASI is not established.

Table 14: To find whether there is correlation between the QTd(cases) and the CLASI

Correlations

		QT dispersion (cases)	CLASI
QT dispersion (cases)	Pearson Correlation	1	.106
	Sig. (2-tailed)		.294
	N	100	99
CLASI	Pearson Correlation	.106	1
	Sig. (2-tailed)	.294	
	N	99	99

Inference:

As ‘r’=0.106 and p=0.294, the relationship between the QTd and CLASI is not established.

Table 15: To find out correlation between the SLEDAI and the CLASI

Correlations

		SLEDAI	CLASI
SLEDAI	Pearson Correlation	1	-.145
	Sig. (2-tailed)		.153
	N	100	99
CLASI	Pearson Correlation	-.145	1
	Sig. (2-tailed)	.153	
	N	99	99

Inference:

As 'r'=-0.145 and p=0.153, the relationship between the SLEDAI and CLASI is not established.

Table 16: To find out correlation between the SLEDAI and ESR

Correlations

		SLEDAI	ESR
SLEDAI	Pearson Correlation	1	.329**
	Sig. (2-tailed)		.001
	N	100	100
ESR	Pearson Correlation	.329**	1
	Sig. (2-tailed)	.001	
	N	100	100

**. Correlation is significant at the 0.01 level (2-tailed).

Inference:

As 'r'=-0.329 and p=0.001, the relationship between the SLEDAI and ESR is positive and statistically significant.

Table 17: To find out correlation between the SLEDAI and Serum Uric Acid

Correlations

		SLEDAI	URIC ACID
SLEDAI	Pearson Correlation	1	.339**
	Sig. (2-tailed)		.001
	N	100	100
URIC ACID	Pearson Correlation	.339**	1
	Sig. (2-tailed)	.001	
	N	100	100

**. Correlation is significant at the 0.01 level (2-tailed).

Inference:

As 'r'=-0.339 and p < 0.01, the relationship between the SLEDAI and serum uric acid is positive and statistically significant.

Table 18 a: Correlation between acute cutaneous lesions and CLASI activity index:

Correlations

		ACUTE CUTANEOUS	CLASI Activity index
ACUTE CUTANEOUS (YES/NO)	Pearson Correlation	1	.289**
	Sig. (2-tailed)		.004
	N	100	100
CLASI Activity index	Pearson Correlation	.289**	1
	Sig. (2-tailed)	.004	
	N	100	100

**. Correlation is significant at the 0.01 level (2-tailed).

Inference :

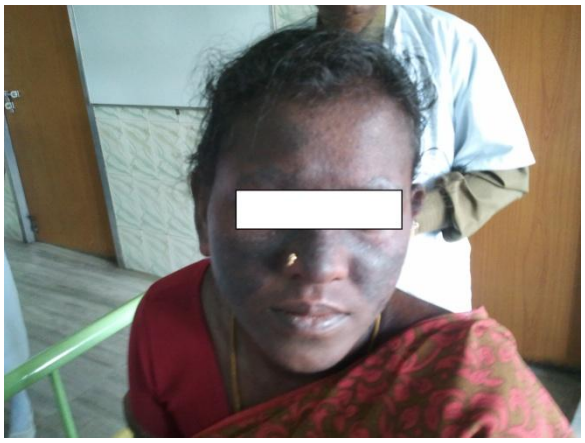
As 'r'=-0.289 and p < 0.01, the relationship between acute cutaneous lesions and CLASI activity index is positive and statistically significant.

Table 18 b: Correlation between acute cutaneous lesions and CLASI damage index:

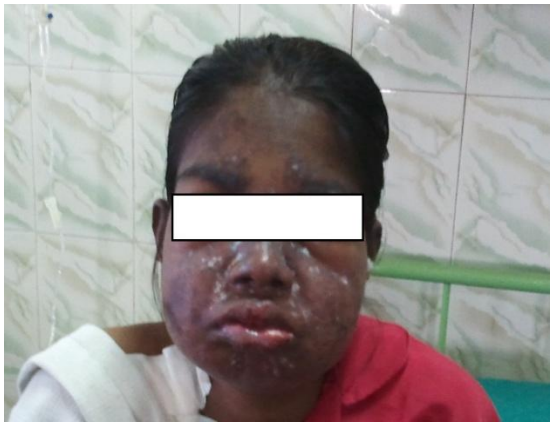
		ACUTE CUTANEOUS	CLASI DAMAGE INDEX
ACUTE CUTANEOUS (YES/NO)	Pearson Correlation	1	.083
	Sig. (2-tailed)		.413
	N	100	100
CLASI DAMAGE INDEX	Pearson Correlation	.083	1
	Sig. (2-tailed)	.413	
	N	100	100

As 'r'=-0.083 and p = 0.413, the relationship between acute cutaneous lesions and CLASI damage index is not statistically significant.

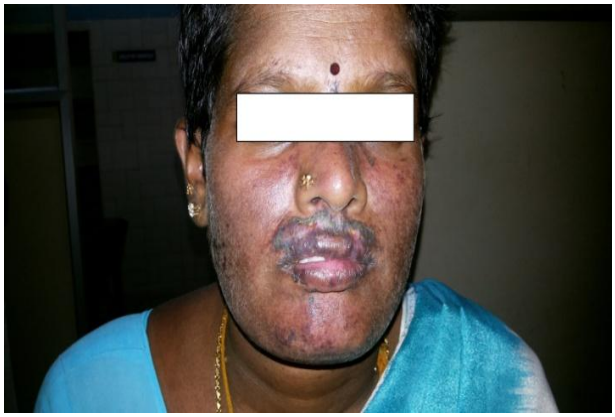
Hence we conclude that the difference in the slope of the trends is insignificant.



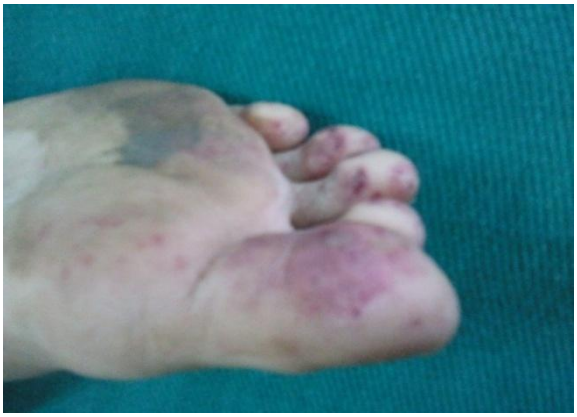
a. Malar rash



b. Malar rash with angioneurotic edema



c. Malar rash with oral mucositis



d. Cutaneous vasculitis

Table 19 a : Correlation between subacute cutaneous lesions and CLASI activity index:

Correlations

		SCLE YES/NO	CLASI Activity index
SCLE YES/NO	Pearson Correlation	1	.595**
	Sig. (2-tailed)		.000
	N	100	100
CLASI Activity index	Pearson Correlation	.595**	1
	Sig. (2-tailed)	.000	
	N	100	100

**. Correlation is significant at the 0.01 level (2-tailed).

Inference :

As 'r'=-0.595 and p < 0.01, the relationship between subacute cutaneous lesions and CLASI activity index is positive and statistically significant.

Table 19 b : Correlation between subacute cutaneous lesions and CLASI damage index:

Correlations

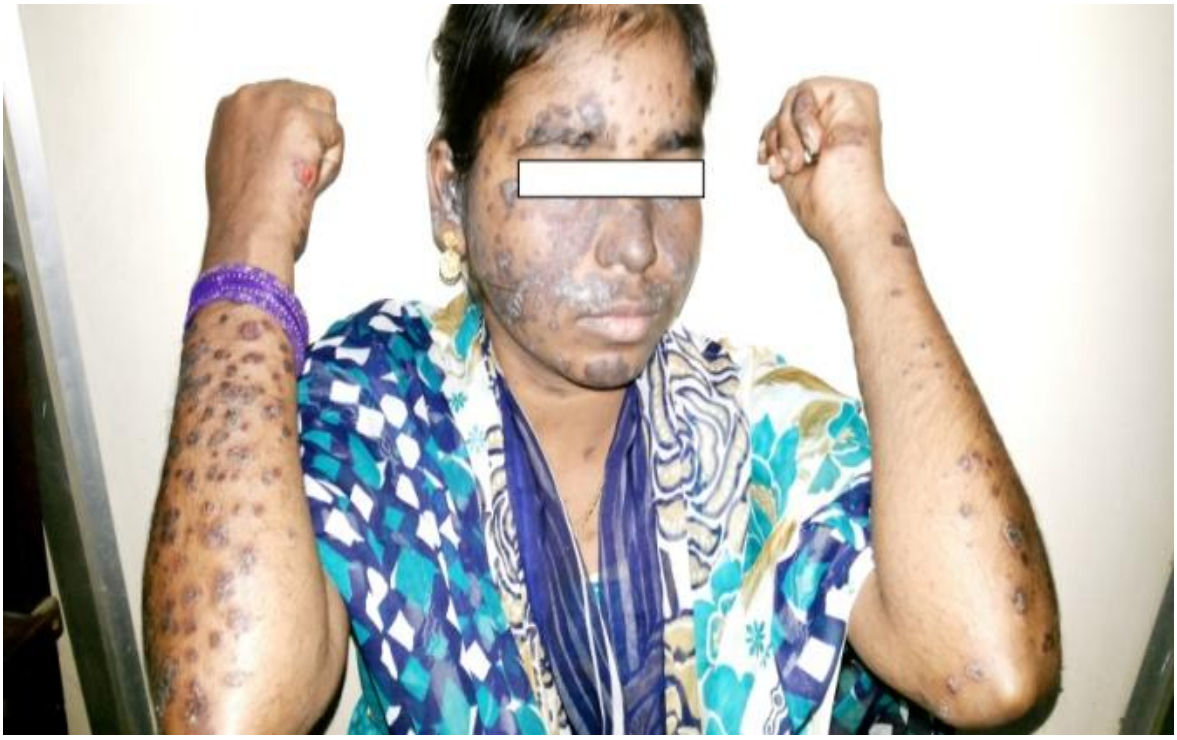
		SCLEY/N	CLASI DAMAGE INDEX
SCLEY/N	Pearson Correlation	1	.415**
	Sig. (2-tailed)		.000
	N	100	100
CLASI DAMAGE INDEX	Pearson Correlation	.415**	1
	Sig. (2-tailed)	.000	
	N	100	100

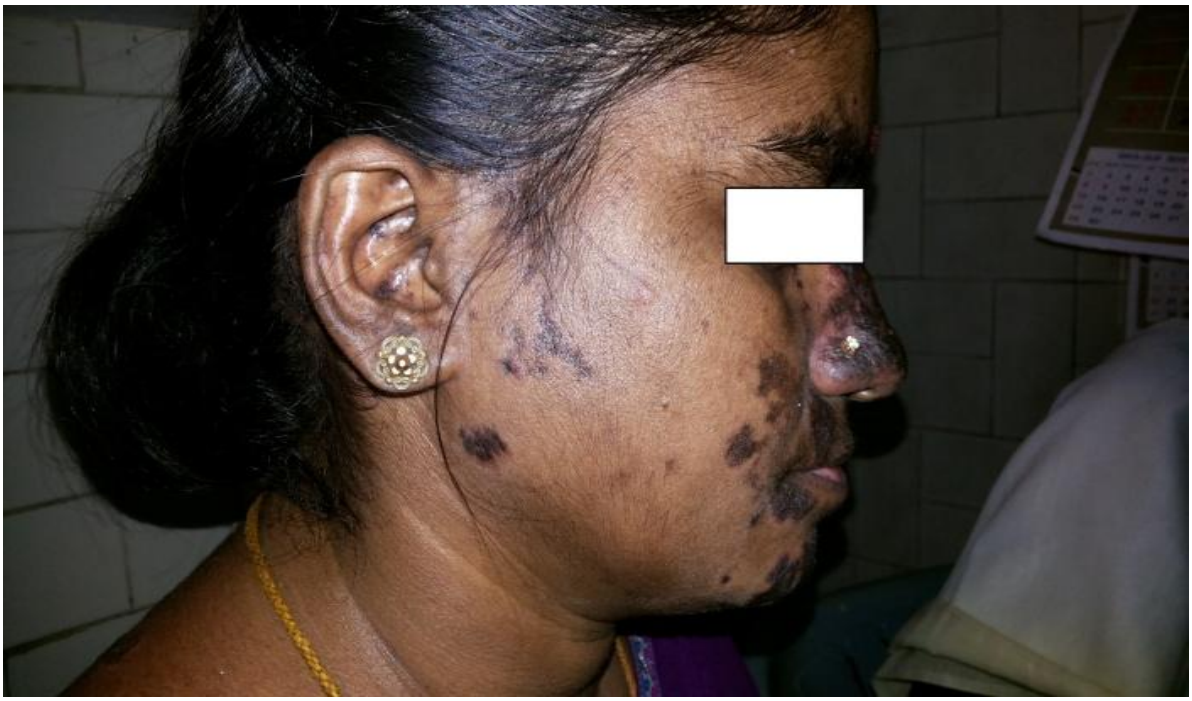
**. Correlation is significant at the 0.01 level (2-tailed).

Inference :

As 'r'=-0.415 and p < 0.01, the relationship between subacute cutaneous lesions and CLASI damage index is positive and statistically significant.

e.Subacute and discoid lesions





f. discoid lesions over face and ears

Table 20 a : Correlation between chronic cutaneous lesions and CLASI activity index:

Correlations

		CHRONIC YES/NO	CLASI Activity index
CHRONIC YES/NO	Pearson Correlation	1	.206*
	Sig. (2-tailed)		.040
	N	100	100
CLASI Activity index	Pearson Correlation	.206*	1
	Sig. (2-tailed)	.040	
	N	100	100

*. Correlation is significant at the 0.05 level (2-tailed).

Inference :

As 'r'=-0.206 and p < 0.05, the relationship between chronic cutaneous lesions and CLASI activity index is positive and statistically significant.

Table 20 b : Correlation between chronic cutaneous lesions and CLASI damage index:

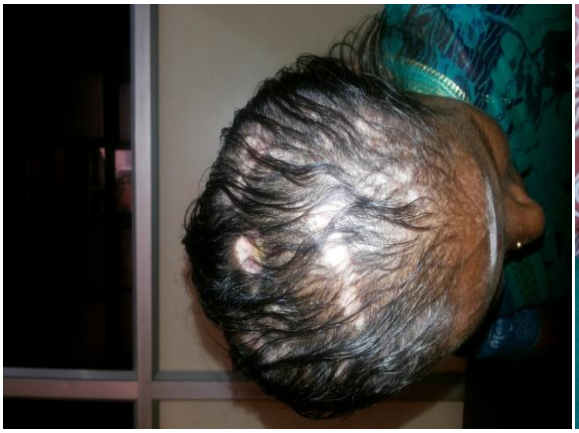
Correlations

		CHRONIC YES/NO	CLASI DAMAGE INDEX
CHRONIC YES/NO	Pearson Correlation	1	.517**
	Sig. (2-tailed)		.000
	N	100	100
CLASI DAMAGE INDEX	Pearson Correlation	.517**	1
	Sig. (2-tailed)	.000	
	N	100	100

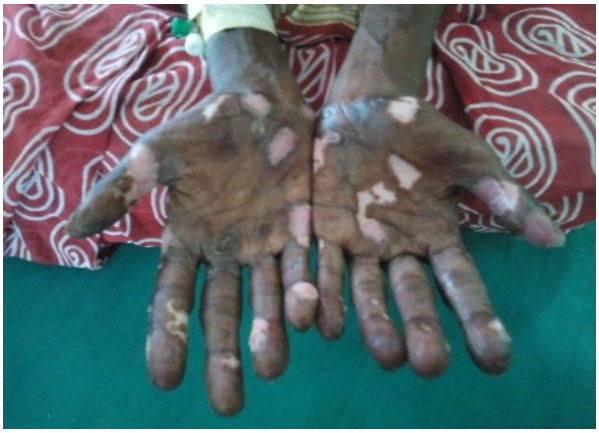
**. Correlation is significant at the 0.01 level (2-tailed).

Inference :

As 'r'=-0.517 and p < 0.01, the relationship between chronic cutaneous lesions and CLASI damage index is positive and statistically significant.

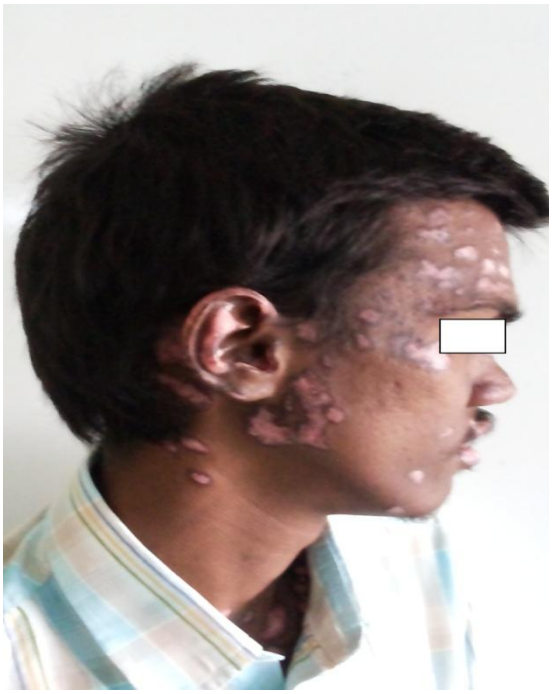


g. Discoid lesions over scalp

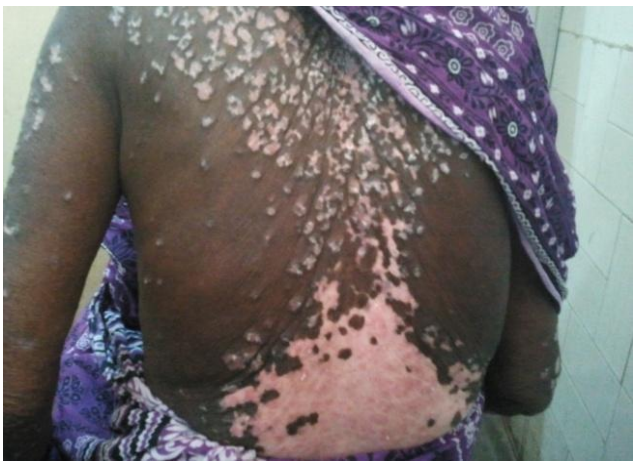


h. Discoid lesions over palms

i.Discoid lesions over scalp



j. Discoid lesions over back (Disseminated discoid)



Discussion

SLE is the typical autoimmune disease with fluctuating disease activity. The disease activity has to be controlled with treatment, for which one has to monitor disease activity. We have various measures like anti ds DNA and complements for assessing disease activity which places a significant financial strain on patients. Hence in this study we studied various parameters which can be used as surrogate markers for assessing disease activity during follow up of SLE patients.

In our study, 100 consecutive patients of SLE getting admitted as in patients were included and their clinical profile, laboratory parameters including immunological investigations were studied. QT interval parameters were studied and compared with age and sex matched controls.

In our study we had 59% of the patients (48% - females & 11% - males) in the age group of 21-30 years and 24% (22% - females & 2% males) of patients in the age group of 17-20 years. The majority of patients were in their 2^{nd} and 3^{rd} decades with an average age of 25.45 years. The female to male ratio in our study was 6:1. In a study done by Renu Saigal et al. the female to male ratio was 11:1.[92] In other Indian studies done by Binoy et al and Malaviya et al the female to male ratio were 19:1 and 8:1.[93,94]The average disease duration in our study was 1.63 years and 2 years in the study done by Renu Saigal et al and 17 months in the study done by Malaviya et al.[92,94]The mean age of onset of disease in our study was 25.45 years and the median age of onset in studies done by Renu Saigal et al and Binoy et al was 27.9 and 21.6 years.[92,93]Other Indian studies done by Malaviya et al and Vaidya et al had a median age of onset of 24 and 26 years. Hence in all Indian studies, the median age of onset was similar.[94,95]

Clinical features	Our study (n = 100) 2014, S.India(Chennai)	Malaviya et al (n = 101) 1985, N.India	Madhavan et al (n = 54) 1983, Madras	Binoy et al (n = 75) 2003 S.India, N.Kerala	Vaidya et al (n = 220) 1997 W.India	Renu Saigal et al (n = 60) 2011 W.India
Fever	81%	44%	11.1%	4.0%	NA	6.7%
Lymphadenopathy	33%	NA	NA	NA	NA	NA
Hepatomegaly/ Splenomegaly	39%	NA	NA	NA	NA	NA
Weight loss	11%	NA	NA	NA	NA	NA
Arthritis	61%	66%	81.4%	89.3%	70.91%	86.7%
Myositis	41%	NA	NA	NA	NA	NA
Cutaneous	58%	85%	62.9%	64%	NA	NA
Cardiovascular	29%	5%	9.2%	5.3%	11.8%	6.7%

Pulmonary	11%	17%	16.6%	8%	15.5%	11.7%
Renal	44%	73%	38.8%	33.3%	35%	56.7%
Neuropsychiatry	45%	15%	20.3%	13.3%	25.5%	13.3%
Hemolytic anemia	29%	NA	NA	0.01%	NA	25%
Leukopenia	26%	16%	3.7%	14.7%	NA	43.3%
Thrombocytopenia	39%	11%	7.4%	12%	NA	33.3%
Serositis	32%	NA	NA	NA	NA	NA
Raynauds	7%	32%	1.8%	2.7%	15.5%	21.&%
ANA	100%	98%	NA	93.3%	NA	98.3%
ds DNA	45%	55%	NA	76%	NA	65%
Complements	72%	NA	NA	NA	NA	NA

QT interval parameters are important prognostic markers for assessing cardiac risk in SLE patients. In our study the mean QTc interval was 436.30 msec (S.D of 27.43) among cases and mean QTd among cases was 44.40msec (S.D 20.61).

	Our study (2014)		**Cardoso et al[10] (2005)**	
	(Cases) (n = 100)	**(Controls) 2014(n = 100)**	**(Cases) (n = 140)**	**(Controls) (n = 37)**
QTc mean	436.30	397.24	427.91	410.05
QTc > 440 ms	51	6	42	0
QTd mean	44.40	39.20	52.38	37.12
QTd >60 ms	6	6	36	2

Both these studies shows increased QTc interval parameters in SLE patients. To our knowledge it is the first study in India to assess these parameters. These ECG changes are found even after excluding patients with baseline ECG abnormalities, systemic hypertension, renal failure and electrolyte abnormalities. Subclinical atherosclerosis or silent myocarditis might be the probable reason for such QTc prolongation in SLE patients.

In our study we also studied the association between QTc prolongation and disease activity (SLEDAI). We found a statistically significant correlation between the two parameters. Then we also assessed the QTc interval of these patients during a flare. Though there was a positive correlation it was not statistically significant except for

severe flare. Like QTc interval we also studied QT dispersion in SLE patients. Though there was a difference in mean value between cases and controls, it was not statistically significant.

In the study done by Cardoso et al QT dispersion values were also significantly prolonged when compared to controls.[10] In another study done by Javad Kojuri et al 124 patients were studied and 20 were excluded. Two groups were made. One with high disease activity (SLEDAI>10) and another with low disease activity (SLEDAI<10). The QT dispersion value in high disease activity group was 58.31 ± 18.66 vs. 47.90 ± 17.41 in low disease activity group with a statistical significance (P<0.004). They also studied the influence of hydroxychloroquine and steroids but found no association but found a significant association between pericarditis, pericardial effusion and disease activity.[2]

QT interval assessment in SLE patients is to detect those with subclinical myocardial involvement and to assess the degree of heterogeneity in cardiac repolarisation. Hence we can identify the individuals with high cardiac risk, screen and treat them aggressively. To our knowledge no previous studies are available which has assessed QT interval parameters during a flare. In severe flare we had a significant association between disease activity and QTc interval. Can QTc interval be used as a marker to assess disease activity? ECG is quite easy to obtain, interpret and is inexpensive. It needs validation with larger studies and has to be compared with Echocardiogarphic parameters and other parameters indicative of subclinical atherosclerosis and has to be done on a larger cohort with follow up during flares.

In a study done by Josiane Bourre Tessier et al, anti Ro antibodies and its association with corrected QT interval was assessed. In the pilot study, 150 subjects

were studied with anti Ro positivity of 38% and QTc was prolonged in 7.3% of subjects. In the second phase 278 subjects were studied and 41% had anti Ro positivity and 6.5% had QTc prolongation. In both the pilot and the second study there was a significant association between QTc interval parameters and anti Ro antibodies.[4]

In our study we found a statistically significant differnce in mean QTc interval between anti Ro antibody positive and negative individuals. But there was no significant correlation between QT dispersion and anti Ro antibody positivity. Similarly there was no association between QT interval parameters and anti La positivity.

In our study we calculated CLASI activity and damage index for the 58 patients with cutaneous involvement. There was no correlation between SLEDAI and CLASI i.e. between systemic activity and cutaneous activity in our study group. We analysed individual types of lesions and their correlation with CLASI activity and damage index. We found a statistically significant correlation between CLASI activity and Acute, Subacute and Chronic type of lesions. Similarly CLASI damage index correlated with subacute and chronic lesions but not with acute lesions.

In a study done by Alakes Kumar Kole et al in Kolkata,150 SLE patients were studied. 30% had cutaneous lesions as the presenting manifestations. Malar rash was the most common (80%), discoid lesion (20%) and subacute lesions the least common(3.34%).[96]

	Our study(n = 100) 2014	Salphale P et al (n = 75) 2011
Mean CLASI activity	10.88	15.4
Mean CLASI damage	5.59	6.87

In the above South Indian study done by Salphale P et al the mean activity and damage scores of CLASI were higher compared to our study. They also found that the scores were more when all three types of lesions were present together and also in patients with extensive skin involvement covering more surface area. The damage index was more in patients with a longer disease duration. [61]

In a study done by Nilay Kanti Das et al, the various cutaneous manifestations were studied to correlate with systemic disease activity. They found that lesions like non scarring alopecia, photosensitivity, oral ulcers and malar rash had significant correlation.[97]

In our study most of the patients had elevated ESR. 41% of them had their ESR between 26 – 50 mm.hr and another 41% between 51 – 75 mm/hr. Only 14% had ESR values above 75 mm/hr. On analyses we found a significant correlation between SLEDAI and ESR. Hence, ESR might be used to assess disease activity indirectly.

In a study done by G Stojan et al, 1865 different patients over 35,373 visits were analysed in a large scale cross sectional study. Though there were a lot of uncertainities over ESR for assessing disease activity, this study strongly proved the association between the two which is in concordance with our study.[69]

In another large scale study LUMINA, there was a significant correlation between ESR and disease activity but had a lot of confounding factors which could influence ESR.[72] Studies done by Mirzayan et al[74] and Chang et al couldn't demonstrate any association between ESR and disease activity but another study done by Nasiri et al showed a significant association.[69, 73]

In our study serum uric acid was elevated in most of the patients with a mean value of 6.13. It had a statistically significant correlation with disease activity. To our knowledge this is the first study correlating serum uric acid levels with disease activity. Other studies done so far have correlated uric acid with lupus nephritis, pulmonary hypertension etc.[81,82]

This study was done in a smaller group of SLE patients and has to be done on a larger scale and the parameters have to be assessed on repeated visits. Most of the patients had high disease activity, as ours was a tertiary referral centre and hence the same can't be extrapolated to the patients in a community. QT interval assessment has its own drawbacks as discussed before. The T waves are quite heterogenous and hence assessment of the exact ending of T wave is difficult and prone to errors. Similarly there are lot of confounding factors which could influence ESR. Even though in our study we could not find any statistical correlation between SLEDAI and CLASI, in our centre we found patients with extensive skin lesions had significant major organ involvement. The individual cutaneous lesions and their relationship with CLASI, SLEDAI and internal organ involvement has to be studied in detail.

Conclusion

- There was a significant difference in mean QTc interval between SLE patients and controls.
- There was a positive correlation between QTc parameters at baseline and during flare but was statistically significant only for severe flare.
- Patients with anti Ro antibody positivity have significant prolongation of QTc interval.
- Patients with high disease activity have significant prolongation of QTc interval.
- There was a significant correlation between ESR and disease activity in SLE.
- There was a significant correlation between serum uric acid and disease activity in SLE.
- This study emphasizes the increased prevalence of probably a subclinical atherosclerosis or myocarditis and hence QTc prolongation in SLE patients with high disease activity.
- Patients with high disease activity and those with anti Ro antibody positivity have to be monitored regularly for increased risk of cardiac arrhythmias and have to be treated promptly.
- In a developing country like ours, where it may be not possible to repeat anti ds DNA and complements during each flare, parameters like QTc interval, ESR and serum Uric acid may be used as surrogate markers to assess disease activity.

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Proforma

Name Age Sex Date

RCC No.

H/o. Present Illness

Past History

Personal History

Treatment History

Family History

General Examination

Pallor Icterus

Cyanosis Clubbing

Lymphadenopathy Pedal Edema

Skin Nails Hair

Weight Height Waist Circumference

Pulse Rate Blood Pressure

Systemic Examination

Cardiovascular System Respiratory System

Abdomen Central Nervous System

Musculoskeletal System Examination

Disease activity scores

SLEDAI

CLASI

Cardiologist opinion

INVESTIGATIONS

Haemogram

Hb TC DC Platelets ESR

Urine routine

Bio-Chemistry

Sugar Urea Creatinine Uric acid

Bilirubin AST ALT SAP

Total Proteins Albumin

Cholesterol Triglycerides LDL VLDL HDL

Urine PCR

Immunological

CRP RF ANA

ANa profile 3 ds DNA

ACL (IgG & IgM) LAC assay(aPTT & DRVVT)

C3 C4 DCT

ECHOCARDIOGRAM

Radiography

Chest X-Ray

ELECTROCARDIOGRAM

HEART RATE

RR INTERVAL

RHYTHM

P WAVE

PR INTERVAL

QRS DURATION

QTc INTERVAL

QT DISPERSION

ST SEGMENT

T WAVE

U WAVE

OTHERS

SLEDAI (Annexure A2)

Descriptor	Definition	Score
Seizure	Recent onset. Exclude metabolic, infectious or drug-related causes	8
Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Includes hallucinations; incoherence; marked loose associations; impoverished thought content; marked illogical thinking; bizarre disorganised or catatonic behaviour. Exclude the presence of uraemia and offending drugs	8
Organic brain syndrome	Altered mental function with impaired orientation or impaired memory or other intellectual function, with rapid onset and fluctuating clinical features. Includes a clouding of consciousness with a reduced capacity to focus and an inability to sustain attention on environment and at least two of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, increased or decreased psychomotor activity. Exclude metabolic infectious and drug-related causes	8
Visual	Retinal changes from systemic lupus erythematosus cytoid bodies, retinal haemorrhages, serous exudate or haemorrhage in the choroid, optic neuritis (not due to hypertension, drugs or infection)	8
Cranial nerve	New onset of a sensory or motor neuropathy involving a cranial nerve	8
Lupus headache	Severe, persistent headache; may be migrainous	8
Cerebrovascular	New syndrome. Exclude arteriosclerosis	8
Vasculitis	Ulceration, gangrene, tender finger nodules, periungal infarction, splinter haemorrhages. Vasculitis confirmed by biopsy or angiogram	8
Arthritis	More than two joints with pain and signs of inflammation	4
Myositis	Proximal muscle aching or weakness associated with elevated creatine phosphokinase/aldolase levels, electromyographic changes, or a biopsy showing myositis	4
Casts	Heme, granular or erythrocyte	4
Haematuria	More than 5 erythrocytes per high power field. Exclude other causes	4
Proteinuria	More than 0.5 g of urinary protein excreted per 24 h. New onset or recent increase of more than 0.5 g per 24 h	4
Pyuria	More than 5 leucocytes per high power field. Exclude infection	4
New malar rash	New onset or recurrence of an inflammatory type of rash	4
Alopecia	New or recurrent. A patch of abnormal, diffuse hair loss	4
Mucous membrane	New onset or recurrence of oral or nasal ulceration	4
Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening	4
Pericarditis	Pericardial pain with at least one of rub or effusion. Confirmation by ECG or echocardiography	4
Low complement	A decrease in CH50, C3 or C4 levels (to less than the lower limit of the laboratory determined normal range)	2
Increased DNA binding	More than 25% binding by Farr assay (to more than the upper limit of the laboratory determined normal range, eg, 25%)	2
Fever	More than 38°C after the exclusion of infection	1
Thrombocytopenia	Fewer than 100 000 platelets	1
Leucopenia	Leucocyte count <3000/mm^3 (not due to drugs)	1

Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) (Annexure A3)

Cutaneous LE Disease Area and Severity Index (CLASI) ©

Select the score in each anatomical location that describes the most severely affected cutaneous lupus-associated lesion

activity ⟵ ⟶ damage

Anatomical Location	Erythema	Scale/ Hypertrophy	Dyspigmentation	Scarring/ Atrophy/ Panniculitis	Anatomical Location
	0-absent 1-pink; faint erythema 2- red; 3-dark red; purple/violaceous/ crusted/ hemorrhagic	0-absent; 1-scale 2-verrucous/ hypertrophic	0-absent, 1-dyspigmentaton	0 – absent 1 – scarring 2 – severely atrophic scarring or panniculitis	
Scalp				See below	Scalp
Ears					Ears
Nose (incl. malar area)					Nose (incl. malar area)
Rest of the face					Rest of the face
V-area neck (frontal)					V-area neck (frontal)
Post. Neck &/or shoulders					Post. Neck &/or shoulders
Chest					Chest
Abdomen					Abdomen
Back, buttocks					Back, buttocks
Arms					Arms
Hands					Hands
Legs					Legs
Feet					Feet

Mucous membrane

Mucous membrane lesions (examine if patient confirms involvement)	
0-absent; 1-lesion or ulceration	

Dyspigmentation

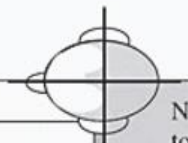
Report duration of dyspigmentation after active lesions have resolved (verbal report by patient – tick appropriate box)

☐ Dyspigmentation usually lasts less than 12 months (dyspigmentation score above remains)

☐ Dyspigmentation usually lasts at least 12 months (dyspigmentation score is doubled)

Alopecia

Recent Hair loss (within the last 30 days / as reported by patient)	
1-Yes 0-No	



NB: if scarring and non-scarring aspects seem to coexist in one lesion, please score both

Divide the scalp into four quadrants as shown. The dividing line between right and left is the midline. The dividing line between frontal and occipital is the line connecting the highest points of the ear lobe. A quadrant is considered affected if there is a lesion within the quadrant.

Alopecia (clinically not obviously scarred)		Scarring of the scalp (judged clinically)	
0-absent 1-diffuse; non-inflammatory 2-focal or patchy in one quadrant; 3-focal or patchy in more than one quadrant		0- absent 3- in one quadrant 4- two quadrants 5- three quadrants 6- affects the whole skull	

Total Activity Score
(For the activity score please add up the scores of the left side i.e. for Erythema, Scale/Hypertrophy, Mucous membrane involvement and Alopecia)

Total Damage Score
(For the damage score, please add up the scores of the right side, i.e. for Dyspigmentation, Scarring/Atrophy/Panniculitis and Scarring of the Scalp)

subjects	age	sex	disease duration	SLEDAI	CLASI Activity	CLASI Damage	CLASI Total	ESR	uric acid	Anti Ro	Anti La	QTc cases	QTd cases	QTc controls	QTd controls	flare	QTc	QTd
s1	18	female	4 years	19	0	0	0	70	7.2	positive		465	20	367	20			
s2	26	female	1 year	23	20	6	26	70	6.2	positive		450	20	360	20	mild	448	20
s3	23	female	5 years	14	0	0	0	52	6.4			377	40	356	40			
s4	18	female	1 year	13	17	10	27	73	6			393	20	408	20	moderate	440	20
s5	19	female	8 months	28	9	0	9	55	3.1	positive		458	40	447	40			
s6	22	female	1 year	11	5	0	5	25	5.4			448	20	429	40	severe	459	40
s7	22	female	1 year	25	4	0	4	60	8.5			465	60	420	40	severe	465	40
s8	20	female	6 months	15	18	4	22	48	5.9	positive		447	20	413	60			
s9	40	female	4 months	9	4	0	4	66	5.8			390	80	436	60	mild	424	40
s10	30	female	2 months	11	6	9	15	44	4.8			408	60	377	60			
s11	38	female	6 months	31	5	0	5	52	7.6			459	20	393	80			
s12	25	female	3 years	9	0	0	0	40	6		positive	424	20	383	20	moderate	436	20
s13	34	female	3 months	14	0	0	0	73	7			380	20	371	20			
s14	22	female	3 months	10	18	10	28	30	5.8	positive		420	40	425	40			
s15	20	female	2 years	7	20	4	24	45	5.6	positive	positive	471	60	436	40			
s16	23	female	2 years	6	36	8	44	28	4.4	positive		450	40	440	40	moderate	459	40
s17	42	female	3 years	15	0	0	0	48	5.6			412	20	429	20			
s18	32	female	1 year	16	0	0	0	55	6.1			440	20	405	60	severe	448	20
s19	53	female	6 months	8	0	0	0	42	6.8	positive		448	80	398	20			
s20	17	female	5 months	13	4	0	4	43	5.2	positive		447	20	425	60			
s21	40	female	3 years	10	2	0	2	40	3.2			362	80	340	20			
s22	18	female	6 months	17	0	0	0	90	6.1		positive	413	40	454	20	severe	426	40
s23	25	female	2 years	25	10	0	10	44	6.2			450	40	425	20			
s24	24	female	1 1/2 years	6	13	0	13	36	8.1	positive		459	20	393	40	moderate	440	20
s25	21	female	2 years	35	2	0	2	54	7			469	40	426	40			
s26	22	female	3 years	27	3	0	3	30	7.2			447	20	408	40	severe	450	40
s27	28	female	6 months	15	5	0	5	44	5.4			377	60	420	20			
s28	18	female	1 1/2 years	10	1	0	1	30	3.4			419	20	347	20			
s29	17	female	6 months	18	0	6	6	40	6.6			447	40	371	20			
s30	23	female	4 years	29	6	6	12	55	5.8			458	40	383	40			
s31	22	female	2 months	24	3	0	3	81	3.8			447	60	360	60			
s32	19	female	6 months	44	10	2	12	64	6.4	positive		458	40	347	80			
s33	23	female	1 year	17	4	0	4	20	4.2			436	80	356	60	mild	393	40
s34	29	female	6 months	8	2	0	2	46	5.6	positive		408	80	408	40			
s35	18	female	5 years	10	20	6	26	36	5.6			450	60	429	40			
s36	26	female	1 year	12	16	4	20	73.3	5.3			400	20	436	20			
s37	19	male	3 months	21	3	0	3	25	4		positive	439	40	356	40	mild	436	40
s38	24	male	1 year	39	12	2	14	50	6.8	positive		465	40	388	20	severe	461	60
s39	32	female	6 months	13	7	1	8	38	5.6	positive		440	40	377	20			
s40	19	female	2 years	12	0	4	4	90	5.6			377	20	360	20			
s41	24	female	3 months	14	3	0	3	52	6	positive		448	80	393	40			

subjects	age	sex	disease duration	SLEDAI	CLASI Activity	CLASI Damage	CLASI Total	ESR	uric acid	Anti Ro	Anti La	QTc cases	QTd cases	QTc controls	QTd controls	flare	QTc	QTd
s42	21	female	1 month	22	2	0	2	36	3.4	positive		439	40	367	40	moderate	454	60
s43	24	female	5 years	11	2	0	2	20	36	positive		420	60	347	40			
s44	48	female	2 years	8	1	0	1	62	6	positive		471	40	360	80			
s45	19	female	1 1/2 months	40	12	4	16	40	6.2			458	40	380	60			
s46	23	male	4 years	28	1	0	1	52	6.4			436	40	405	60			
s47	30	male	4 months	20	4	0	4	56	5.8	pos		436	20	400	60			
s48	24	male	8 months	13	1	0	1	35	4.2			408	40	413	40			
s49	29	male	1 month	16	0	0	0	70	6.8	pos		436	60	340	40			
s50	34	male	4 months	24	0	0	0	55	7.2	pos		465	80	380	20	severe	469	60
s51	19	male	6 months	16	0	0	0	48	5.6	pos		414	20	360	40			
s52	21	male	3 months	27	3	0	3	35	6.4	pos		459	60	388	20			
s53	23	male	4 months	19	7	2	9	65	6.8	pos		425	40	390	40			
s54	26	male	6 months	11	16	3	19	45	5.1	pos	positive	450	40	380	60			
s55	27	male	6 months	10	4	8	12	50	4.2	pos		436	40	419	40			
s56	28	male	1 year	39	12	4	16	140	6.4	pos		461	40	420	20			
s57	29	female	2 years	16	20	14	34	44	5.6			388	40	380	40			
s58	33	female	3 years	16	1	0	1	56	6.8			447	20	340	40	severe	471	40
s59	26	female	4 years	16	2	0	2	78	6.2			429	80	360	40			
s60	19	female	2 years	12	16	8	24	54	5.8	pos		465	80	367	80			
s61	19	female	6 months	9	8	22	30	45	4.2			420	80	377	20			
s62	21	female	3 months	32	8	0	8	90	7.1			471	60	383	40			
s63	28	female	1 year	20	2	0	2	54	6			419	40	371	40	moderate	424	20
s64	45	female	1 year	19	0	0	19	66	6.8			440	60	356	40	moderate	436	40
s65	18	female	6 months	20	0	0	0	32	4.2			401	40	436	60			
s66	18	female	4 months	30	20	12	32	75	6.8			447	60	429	40			
s67	24	female	2 years	28	2	0	2	60	6			448	60	402	60			
s68	21	female	2 years	14	0	0	0	38	5		positive	429	20	424	40			
s69	29	female	3 months	34	2	0	2	34	4.4	pos		458	20	436	60			
s70	23	female	6 months	41	8	2	10	88	7	pos		454	20	414	40			
s71	29	female	1 1/2 years	43	12	4	16	90	6.8	pos		461	40	408	20			
s72	30	female	2 years	25	0	0	0	54	6.1	pos		459	20	377	20	mild	440	40
s73	21	female	6 months	29	0	0	0	30	7.2			426	80	393	20			
s74	36	female	3 months	23	8	0	8	80	6.8	pos		401	40	383	20			
s75	24	female	6 months	29	4	4	8	64	5.4			439	60	388	20			
s76	24	male	1 year	21	4	0	4	40	6.4	pos		458	60	419	40	moderate	454	40
s77	28	female	6 months	25	2	0	2	60	5.8	pos	positive	481	60	408	20			
s78	26	female	1 year	24	6	2	8	54	6	pos		436	40	347	40			
s79	24	female	6 months	43	4	0	4	78	6.4	pos		448	20	425	20			
s80	22	female	1 1/2 years					32	4.2			360	40	436	20			
s81	24	female	6 months	21	1	0	1	134	6.8	pos		471	40	408	20			
s82	21	female	7 months	5	14	6	20	80	5.6	pos		450	40	356	60			

subjects	age	sex	disease duration	SLEDAI	CLASI Activity	CLASI Damage	CLASI Total	ESR	uric acid	Anti Ro	Anti La	QTc cases	QTd cases	QTc controls	QTd controls	flare	QTc	QTd
s83	29	female	3 years	21	1	0	1	110	4.8	pos		426	40	388	80			
s84	21	female	3 years	24	4	0	4	31	7.3		positive	439	40	429	60	severe	440	40
s85	21	female	2 months	36	8	0	8	73	5.7	pos		450	80	367	60			
s86	19	female	6 months	22	30	14	44	54	6.2	pos		465	80	380	20			
s87	19	female	1 year	23	8	0	8	44	5.8			398	60	401	40			
s88	24	female	8 months	15	4	4		60	5.2	pos		426	20	412	20			
s89	17	female	1 1/2 years	31	2	0	2	42	6.4	pos		458	20	459	40	moderate	454	60
s90	39	female	1 year	17	6	8	14	30	5.6			400	20	426	20			
s91	24	female	4 years	21	1	0	1	60	5.8			388	40	469	40			
s92	18	female	2 years	13	18	10	28	44	4.2	pos	positive	454	40	454	20			
s93	21	female	3 years	23	2	0	2	54	5.6			471	20	475	40			
s94	34	female	1 year	11	14	14	28	60	6		positive	459	40	436	20			
s95	18	female	3 months	24	8	6	14	74	6.4			426	80	371	60	mild	436	40
s96	32	female	8 months	25	3	0	3	54	5.8	pos		459	60	377	80			
s97	28	female	6 months	9	12	10	22	36	4.8	pos		471	80	429	60			
s98	26	female	1 1/2 years	34	4	0	4	70	6.8			465	80	383	40	mild	450	40
s99	29	female	2 years	38	10	2	12	80	6.4			414	40	393	40			
s100	33	female	6 months	16	12	8	20	65	5.6			420	40	408	40			

PATIENT CONSENT FORM

Title of the Project

A STUDY ON QT INTERVAL IN PATIENTS WITH SLE AND ITS CORRELATION WITH DISEASE ACTIVITY AND AUTOANTIBODIES

Institution : **Department of Rheumatology,**
Madras Medical College, Chennai-600 003.

Name	:	Date	:
Age	:	IP No	:
Sex	:	RCC No	:

The details of the study have been provided to me in writing and explained to me in my own language.

I confirm that I have understood the above study and had the opportunity to ask questions.

I understood that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without the medical care that will normally be provided by the hospital being affected.

I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s).

I have been given an information sheet giving details of the study.

I fully consent to participate in the above study.

Signature of Participant

INFORMATION SHEET

We are conducting a study on Systemic Lupus Erythematosus among patients attending Government General Hospital, Chennai and for that your Co-operation may be valuable to us.

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time ; your decision will not result in any loss of benefits to which you are otherwise entitled.

The result of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of Investigator
Date

Signature of Participant
Date

ஆராய்ச்சி ஒப்புதல் படிவம்

ஆராய்ச்சி தலைப்பு

பல்லுறுப்பு அழற்சி நோய் (லூபஸ்)

ஆராய்ச்சி நிலையம் : **இராஜீவ் காந்தி அரசு பொது மருத்துவமனை,** சென்னை-3.

பெயர் : வயது :

ஆராய்ச்சி சேர்க்கை எண் : தேதி:

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 உடல்நலம் பாதிக்கப்பட்டாலோ அல்லது வழக்கத்திற்கு மாறான நோய்க்குறி தென்பட்டாலோ உடனை அதை மருத்துவ அணியிடம் தெரிவிப்பேன் என்று உறுதி அளிக்கிறேன். ☐

.....	.....	.....
பங்கேற்பாளர் பெயர்	கையொப்பம்/ கைரேகை	தேதி

.....	.....	.....
ஆராய்ச்சியாளரின் பெயர்	கையொப்பம்	தேதி

<u>ஆராய்ச்சி தகவல் தாள்</u>

தலைப்பு

பல்லுறுப்பு அழற்சி நோய் (லூபஸ்)

சென்னை இராஜீவ்காந்தி அரசு பொது மருத்துவனையில் பல்லுறுப்பு அழற்சி நோய் (லூபஸ்) பற்றிய ஆய்வு இங்கு நடைபெறுகிறது.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க விரும்புகிறோம். அதனால் தங்களது நோயின் ஆய்வறிக்கையோ அல்லது சிகிச்சையோ பாதிப்பு ஏற்படாது என்பதையும் தெரிவித்துக் கொள்கிறோம்.

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

இந்த சிறப்பு சிகிச்சையின் முடிவுகளை ஆராய்ச்சியின்போது அல்லது ஆராய்ச்சியின் முடிவின் போது தங்களுக்கு அறிவிக்கப்படும் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

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

.....	.....	.....
பங்கேற்பாளர் பெயர்	கையொப்பம்/ கைரேகை	தேதி

.....	.....	.....
ஆராய்ச்சியாளரின் பெயர்	கையொப்பம்	தேதி

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3
Telephone No : 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr.S.Sham,
PG in DM Rheumatology.
MMC,Chennai – 3.

Dear S.SHAM

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled "The impact of disease activity on QT interval in patients with SLE and its correlation with Auto antibodies" No.19032013.

The following members of Ethics Committee were present in the meeting held on 05.03.2013 conducted at Madras Medical College, Chennai -3.

1. Dr.SivaKumar, MS FICS FAIS --- Chairperson
2. Prof. R. Nandhini MD -- Member Secretary
   Director, Instt. of Pharmacology ,MMC, Ch-3
3. Prof. Shyamraj MD -- Member
   Director i/c , Instt. of Biochemistry , MMC, Ch-3
4. Prof. P. Karkuzhali. MD -- Member
   Prof., Instt. of Pathology, MMC, Ch-3
5. Prof. A. Radhakrishnan MD -- Member
   Prof of Internal Medicine, MMC, Ch-3
6. Prof. S. Deivanayagam MS -- Member
   Prof of Surgery, MMC, Ch-3
7. Thiru. S. Govindsamy. BABL -- Lawyer
8. Tmt. Arnold Saulina MA MSW -- 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, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

R Nadini

Member Secretary, Ethics Committee

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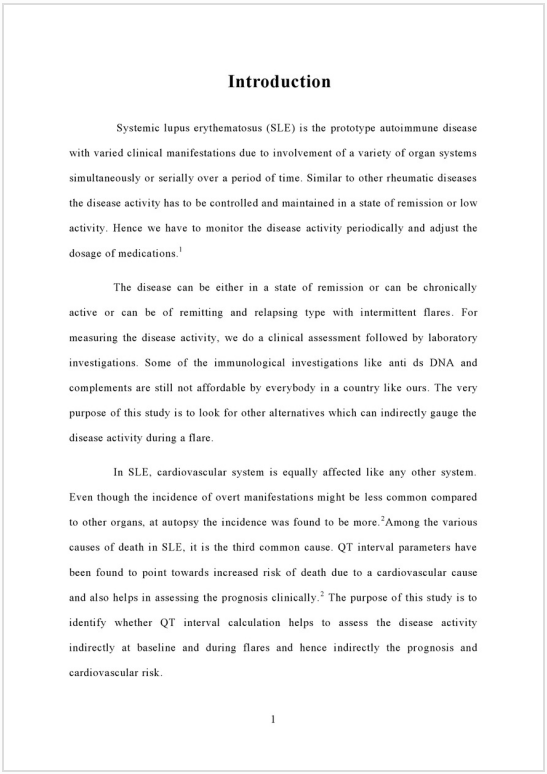


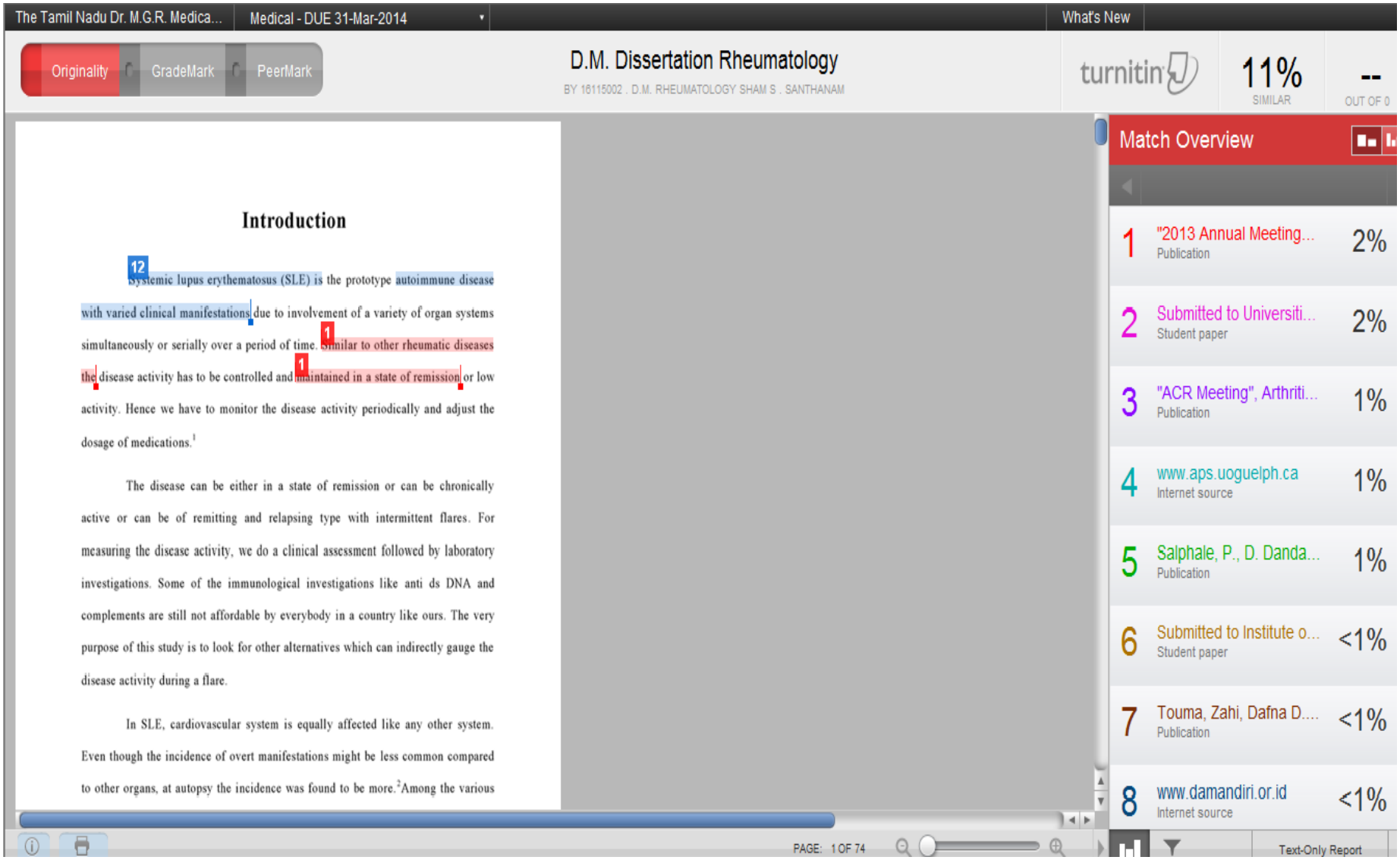
Introduction

Systemic lupus erythematosus (SLE) is the prototype autoimmune disease with varied clinical manifestations due to involvement of a variety of organ systems simultaneously or serially over a period of time. Similar to other rheumatic diseases the disease activity has to be controlled and maintained in a state of remission or low activity. Hence we have to monitor the disease activity periodically and adjust the dosage of medications.[1]

The disease can be either in a state of remission or can be chronically active or can be of remitting and relapsing type with intermittent flares. For measuring the disease activity, we do a clinical assessment followed by laboratory investigations. Some of the immunological investigations like anti ds DNA and complements are still not affordable by everybody in a country like ours. The very purpose of this study is to look for other alternatives which can indirectly gauge the disease activity during a flare.

In SLE, cardiovascular system is equally affected like any other system. Even though the incidence of overt manifestations might be less common compared to other organs, at autopsy the incidence was found to be more.[2]Among the various causes of death in SLE, it is the third common cause. QT interval parameters have been found to point towards increased risk of death due to a cardiovascular cause and also helps in assessing the prognosis clinically.[2] The purpose of this study is to identify whether QT interval calculation helps to assess the disease activity indirectly at baseline and during flares and hence indirectly the prognosis and cardiovascular risk.

1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Introduction
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