"A STUDY ONTHE ASSOCIATION OF CLINICAL PROFILE WITH THE OUTCOMES OF LUPUS NEPHRITIS"

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CERTIFICATE

This is to certify that this dissertation entitled **"A study on the association of clinical profile with the outcomes of lupus nephritis"** presented here is original work done by **Dr.S.VIDYA**, DM Post Graduate in the Department of Rheumatology, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai-600003 in partial fulfillment of the university rules and regulation for the award of D.M.BranchIX- Rheumatology, under my guidance and supervision during the academic period from 2010-2013.

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DECLARATION

I, **Dr.S.VIDYA**hereby solemnly declare that this dissertation entitled **"A study on the association of clinical profile with the outcomes of lupus nephritis"** was done by me in the Department of Rheumatology, Madras Medical College & Rajiv Gandhi Govt. General Hospital, Chennai-3 during February 2011 to February 2013 under the guidance and supervision of Prof.Dr.S.Rukmangatharajan, MD., DM., FMMC., This dissertation is submitted to the Tamil Nadu Dr.M.G.R.Medical University towards the partial fulfillment of requirement for the award of D.M., Degree in Rheumatology.

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INDEX

ABBREVIATIONS

LN - Lupus Nephritis

SLE - Systemic Lupus Erythematosus

HLA - Human Leucocyte Antigen

EULAR - European League Against Rheumatism

ERA/EDTA - European Renal Association / European Dialysis and Transplant Association

ISN/RPS - International Society of Nephrology/ Renal Pathology Society

CR - Complete Response

PR - Partial Response

IMP - Improved

REF - Refractory

LTF - Lost follow up

NIH - National Institute of Health

ELNT - Euro Lupus Nephritis Trial

CYC - Cyclophosphamide

AZA - Azathioprine

MMF - MycophenolateMofetil.

ANA - Anti Nuclear Antibody

ACL - Anti Cardio Lipin

LAC - LupusAnti Coagulant

ESRD - End Stage Renal Disease

INTRODUCTION

Sytemic lupus erythematosus is a paradigmatic autoimmune disorder, the manifestations of which are protean sparing few organ systems if any.[1] Such diversity is attributed to its etiopathogenesis wherein antibodies to the components of cell nucleus have been implicated. One major cause of morbidity and utilization of health resources is renal involvement. More than half of the mortality in SLE is due to renal involvement.[2-5]

As with SLE, heterogeneity, both clinical as well as histological is the hall mark of lupus nephritis. The disease usually is asymptomatic in its earlier course thus vigilant screening of SLE patients for renal involvement remains the important step in reducing the mortality and morbidity.

Even though recent treatments are effective and have reduced the adverse outcomes the therapeutic options are limited and induce toxicities in the long term. [6,7] Hence there is a need to identify patients who may have a worse prognosis so that aggressive treatment can be instituted early.

Prognosis and therefore treatment decisions vary greatly according to the clinical and pathological forms of lupus nephritis. [8-10] Each individual has a unique combination of these. Even though individual factors vary in their impact,

the greater the number of factors with worse prognosis, the less the patient is likely to respond to therapy and hence needs aggressive therapy.

Considering the above mentioned prognostic factors may help in improving clinical decision making regarding the type and intensity of immune suppressive treatment for patients with lupus nephritis.

Studies of long term prognosis in lupus nephritis have focused on risk factors which are present either at the onset or those that develop during the course of the illness. These predict the mortality over subsequent 10 years. The results of these studies may vary but they are useful as they inform us about how specific manifestations influence the outcome. But these are less helpful in making treatment decisions than studies of short term prognosis as short term outcome studies are more likely influenced by timely intervention.

In spite of many years of intense investigations controversies surrounding the importance of clinical, demographic, laboratory and histologic features in predicting renal outcomes continue to evolve as current and recent treatments have altered the prognostic significance of these factors that were previously considered significant.

Here in this study we have tried to assess the outcomes of lupus nephritis in fifty patients and the association of clinical and immunologic profile with these outcomes has been studied.

AIMS AND OBJECTIVES

1. To study the outcomes of lupus nephritis in 50 patients during the study period.

2. To study the association of demographic, clinical, laboratory, histopathologic and treatment profile of these patients with the outcome.

3. To compare the results with the standard data available.

REVIEW OF LITERATURE

EPIDEMIOLOGY:

Lupus nephritis affects 40-70% of patients with SLE.[11]The frequency of lupus nephritis peaks during the first two years since the onset of SLE and its incidence follows a decrescendo pattern reaching a trough after five years of SLE. Asymptomatic urine abnormalities like proteinuria or hematuria is seen in half the cases. In about 30% nephrotic or nephritic syndrome occurs. Chronic renal insufficiency or rapidly progressive glomerulonephritis occur in less than 5% of the individuals.

PATHOGENESIS:

Only a few diseases like lupus nephritis are characterized by immune complexes detected in all four renal components namely glomeruli, tubules, interstitium and blood vessels.[12] Although IgG is the dominant immunoglobulin (98%) co-deposits of IgM and IgA are also common. The term 'full house' staining is applied when all the three immunoglobulin classes are present.

Intraglomerular inflammation and recruitment of leukocytes are the earliest events in kidney that follow immune complex formation and their deposition. Activation and proliferation of resident renal cells soon follow the initial events. Fibrinoid necrosis occurs due to the destruction of renal cells by

necrosis or apoptosis. In the event of lesser injury there is proliferation of endocapillary cells and production of extracellular matrix. Rupture of capillary wall and even the capsule itself occurs in case of severe injury resulting in accumulation of fibrin over basement membrane along with collagen, mononuclear cells and epithelial cells in the urinary space resulting in crescentic glomerulonephritis pattern. Atrophy and scarring is the end result of protracted inflammation.

The histopathology and the intensity of the inflammatory response are closely linked to the location of immune complex deposition and formation. Mesangial lupus nephritis occurs when immune complexes are deposited in mesangium. Focal or diffuse proliferative lupus nephritis with profuse glomerular hypercellularity occurs when immune complexes are deposited in the subendothelial region. Proliferation of endothelial and mesangial cells hand in hand with leukocytic infiltrates is the cause for this hypercellularity the result of which is compromised capillary flow and renal function. Membranous nephropathy occurs when there are epimembranous (subepithelial) deposits along diffusely thickened peripheral glomerular capillary loops and lack of inflammatory infiltrates.

The differences in the composition and properties of the immune complexes such as size, specificity, charge and immunoglobulin isotype probably explain the diverse morphological expressions of lupus nephritis. An intermediate sized, high avidity small immune complex favours a mesangial pattern while large sized loads can spill into the subendothelial region. Low avidity, smaller, cationic complexes that dissociate and reform in situ favors sub epithelial deposits.

Traditional thinking is that lupus nephritis is a quintessential type III hypersensitivity reaction with deposition of immune complexes in the glomeruli and subsequent complement activation.[13] Recently emphasis is also given to the significance of local formation of immune deposits.[14] Positively charged nucleosomes are attracted towards the negatively charged sites in the glomerular wall. After getting implanted in the glomerular filter these auto antigens form immune complexes after reacting with the circulating auto antibodies.

Auto antibodies to normal glomerular constituents like laminin, heparan sulfate, type IV collagen are also implicated in another theory of in situ immune complex formation. The role of antigen presentation by T cells, activated macrophages and Fcγ receptor (FcγR) bearing monocytes are important in glomerulonephritis.[15-17] Mice deficient in FcγR are immune to development of glomerulonephritis but not to immune complex deposition.[18]

GENETICS:

This can be divided in to HLA and non HLA genes. HLA genes implicated in lupus nephritis are HLADRB1*1501/DQB1*0602, DQB1* 0201, DQB1*0301, DR2/DR3. Homozygous deficiencies of early complement components have also been implicated.[19]

COMPLEMENT SYSTEM :

The role of complement system in the pathogenesis of lupus nephritis cannot be under estimated. Presence of complement activation factors in tubules, glomerulus, interstitium and urine provides support for this. Though classical component pathway deficiency is viewed as a predisposing factor for lupus nephritis, great majority of patients have intact alternative especially lectin pathway. Evidences favouring the role of complement pathway include findings that an inhibitory anti-C5 mAb hinders the onset of glomerulonephritis in the (NZB x NZW) F1 model of SLE. The fact that *fB*-/- and *fD*-/-MRL/*lpr* mice are immune from lupus nephritis also underscores the importance of alternate pathway.

Though role of complement activation is traditionally restricted to glomerular disease, additional roles in tubulointerstitial inflammation and proteinuric states have also been suggested. When complement activation components enter the urinary space after a break in basement membrane they are

capable of being activated since the tubular epithelium lacks complement regulatory proteins.

ROLE OF ANTI-ds DNA:

Anti-ds-DNA antibodies are present in about 60% of patients with SLE. Specifically they are associated with nephritis which has the strongest correlation with it.[20] Lot of evidence suggests the role of DNA-anti DNA complexes in the pathogenesis of LN.[21] This includes detection of anti-DNA antibodies in the kidneys, free DNA in the plasma, alterations in the serum concentrations of anti DNA antibodies and complement. The theory of molecular mimicry has also been implicated wherein anti ds DNA may react with glomerular and mesangial target antigens such as alpha actinin, a matrix protein. Not all patients with high anti ds DNA develop nephritis. Anti-DNA measurements may help in monitoring disease activity. Sometimes anti-DNA and complement (C3, C4) levels vary reciprocally over time.[22,23] ELISA and *Crithidia luciliae* kinetoplast staining assay detect low affinity interactions whereas Farr assay, which detects high-affinity antibodies, may predict disease activity more accurately and may increase 10 or more weeks before a flare.

ROLE OF APS NEPHROPATHY:

Anti-phospholipid antibodies are implicated in the pathogenesis of a unique type of vascular nephropathy (APSN).Features of APSN are present in 20% to 30% of patients with SLE.[24] They are fibrous occlusions of arteries/arterioles, organizing thrombi with recanalisation, thrombotic microangiopathy, focal cortical atrophy and chronic lesions such as fibrous intimal hyperplasia.[25, 26]

CLINICAL FEATURES:

Lupus nephritis is usually asymptomatic unless it is advanced nephrotic syndrome or renal failure. It is usually discovered during a routine evaluation. Proteinuria, presence of urinary casts, hematuria, pyuria, increased serum creatinine and hypertension are the features most commonly seen . Specifically the revised criteria for classification for SLE includes a) Persistent proteinuria > 0.5 g per day or > than 3+ if quantitation not performed, OR

b) Cellular casts: red cell, hemoglobin, granular, tubular, or mixed as evidence of renal disease.Hematuria (>5 RBCs/HPF),pyuria (>5WBCs/HPF) in the absence of infection and raised serum creatinine concentration have also been recognized as the renal manifestations. Hence urine analysis must be performed regularly in addition to serum creatinine.

RENAL BIOPSY

Renal biopsy is necessary to identify the type of kidney involvement as patient management is determined based on it.[27,28] Most patients with lupus nephritis have abnormal renal biopsy either on light microscopy or special techniques like immunofluorescence or electron microscopy.

Renal involvement is not only limited to glomerulonephritis but may also be due to interstitial nephritis, tubular disease, vasculitis, arteriolosclerosis, thrombotic microangiopathy, and lupus vasculopathy. There may be changes secondary to co-morbidities such as human immunodeficiency virus (HIV) infection. A semi quantitative analysis of specific histologic features based on a 0-3 scale) is included into the elements of the activity and chronicity indices.

The International Society of Nephrology/Renal Pathology Society revised the earlier World Health Organization classification in 2003 for a better description and standardization of the lesions seen on biopsy. The classification is based on the changes observed on light microscopy, immunofluorescence staining, and electron microscopy.[29] In a study of 46 japenese patients Yakohama et al found that ISN /RPS 2003 has better prognostic value.[30]

INDICATIONS FOR RENAL BIOPSY IN LUPUS NEPHRITIS

INITIAL BIOPSY (before treatment)

Nephritic urine sediment (glomerular hematuria and cellular casts).

Glomerular hematuria with proteinuria >0.5 to 1.0 gm/day.

Glomerular hematuria with proteinuria <0.3 to 0.5 gm/day and low C3 and/ or positive anti-ds DNA.

Proteinuria >1.0 to 2.0 gm/day (especially if C3 is low and/or positive anti-ds DNA).

REPEAT BIOPSY (during or after treatment)

Unexplained worsening of proteinuria (>2 gm/day increase if non nephrotic at baseline, or >50% increase if nephrotic).

Unexplained worsening of renal function (reproducible ≥30% increase in serum creatinine).

Persistent glomerular hematuria with proteinuria >2 gm/day or proteinuria >3 gm/day (especially if C3 is decreased).

Nephritic or nephrotic flare.

According to recent EULAR/ ERA-EDTA guidelines any renal involvement is considered an indication for renal biopsy.

ACTIVITY AND CHRONICITY INDICES *

Activity index (lesions are scored 0-3 with maximum score 24 points)

* Hypercellularity: endocapillary proliferation compromising glomerular capillary loops
* Leukocyte exudation: polymorphonuclear leukocytes in glomeruli
* Karyorrhexis/fibrinoid necrosis (weighted ×2): necrotizing changes in glomeruli
* Cellular crescents (weighted ×2): layers of proliferating epithelial cells and monocytes lining Bowman capsule
* Hyaline deposits: eosinophilic and PAS-positive materials lining (wire loops) or filling (hyaline thrombi) capillary loops
* Interstitial inflammation: infiltration of leukocytes (predominantly mononuclear cells) among tubules

Chronicity index (lesions are scored 0-3 with maximum score 12 points)

* Glomerular sclerosis: collapse and fibrosis of capillary tufts
* Fibrous crescents: layers of fibrous tissue lining Bowman capsule
* Tubular atrophy: thickening of tubular basement membranes, tubular epithelial degeneration, with separation of residual tubules
* Interstitial fibrosis: deposition of collagenous connective tissue among tubules

(* Scored on a scale of 0-3 representing either (a) absent, mild, moderate, and severe lesions or (b) the presence of lesions in none, <25%, 25% to 50%, and 50% of glomeruli , respectively.)

Table 1- ISN/RPS CLASSIFICATION OF LUPUS NEPHRITIS

Class I	Minimal mesangial lupus nephritis Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence
Class II	Mesangial proliferative Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposits A few isolated subepithelial or subendothelial deposits may be visible by immunofluorescence or electron microscopy, but not by light microscopy
ClassIII	Focal lupus nephritis Active or inactive focal, segmental, or global endocapillary or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations
Class IV	Diffuse lupus nephritis Active or inactive diffuse, segmental or global endocapillary or extracapillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class is divided to *diffuse segmental* (IV-S) lupus nephritis when ≥50% of the involved glomeruli have segmental lesions and *diffuse global* (IV-G) when ≥50% of the involved glomeruli have global lesions. Segmental is defined as a glomerular lesion that involves less than half of the glomerular tuft. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation
Class V	Membranous lupus nephritis Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations Class V nephritis may occur in combination with class III or class IV, in which case both will be diagnosed Class V nephritis may show advanced sclerotic lesions
Class VI	Advanced sclerotic lupus nephritis ≥90% of the glomeruli globally sclerosed without residual activity

Renal biopsy may show hematoxylin bodies, the tissue equivalent of LE cell phenomenon. Mesangial lupus nephritis characterized by the accumulation of immune complex deposits within the mesangium (class I) and its futher progression in to mesangial hypercellularity (class II) are at the milder end of the spectrum of the renal lesions. Most people with mesangial lupus nephritis are clinically silent and respond well to renoprotective therapies even without aggressive immunosuppressive regimens though on occasions they may have severe renal involvement and validate aggressive therapy. Lupus nephritis is further classified as focal or diffuse depending on the percentage of glomeruli involved with subendothelial deposits, i.e. class III (<50% involved) and class IV (≥50% glomeruli involved) respectively. They are further described according to the chronicity of the lesions. Membranous lesions (class V) are characterized mainly by subepithelial deposits.They may also have mesangial involvement. Advanced sclerosis (class VI) is the end stage or "burnt out" phase of lupus nephritis. Lupus vasculopathy is characterized by the presence of hyaline thrombi within the arteriolar lumen and/or intralobular arteries. Tubulointerstitial disease involves tubular basement membrane atrophy. Other findings that may also be seen in lupus are lupoid nephrosis, focal segmental glomerulosclerosis, IgM nephropathy and amyloidosis. [31]

EVALUATION

ASSESSMENT OF RENAL INVOLVEMENT:

The basic assessment of renal function requires screening for proteinuria, hematuria, leukocyturia and nitrates to check for infections using a urine dipstick. While assessing hematuria other conditions like infections, calculi and menstrual blood loss must be excluded. Urine casts still remain an important indicator of active renal disease. Analysis of a 24 hr urine specimen is more useful than a urine dipstick or serum creatinine. Protein/creatinine ratio or albumin creatinine ratio and glomerular filtration rate (GFR) are also becoming important tools especially in clinical trials as these require little patient cooperation and are more robust measurements. Renal biopsy remains the best way to distinguish renal activity from damage and to establish the type of renal involvement.

The use of serological tests in assessing lupus activity has long been debated.[32] Anti ds DNA antibodies are present in 60% of lupus patients making its measurement useful only in those with positive antibodies. Usually the levels rise during the development of a flare. But it may fall during peak clinical activity because of tissue deposition. Changing levels of ds DNA antibodies must be viewed with caution especially before reducing therapy. Decreasing levels of complements C3 or C4 are usually the forerunner of a renal flare. So are the raising levels of complement degradation products C3d or C4d.

MONITORING DISEASE ACTIVITY

URINALYSIS:

Urinalysis is the most useful method to detect and monitor disease activity in lupus nephritis. The urine sample must be fresh, early morning, mid stream, clean catch and non refrigerated. Presence of hematuria (usually microscopic) indicates inflammatory glomerular or tubulointerstitial involvement. Granular and fatty casts indicate proteinuric states while cellular casts involving RBCs, WBCs or mixed pattern are indicators of nephritic states. Severe glomerular and tubular ongoing disease can cause 'telescopic urine sediment' i.e. containing full range of cells and casts. Resolution of urine sediments is a feature of renal remission provided it is sustained. Reappearance of cellular casts when associated with proteinuria is a very early predictor of renal flare and may precede anti ds DNA titers or decreased complement levels. Spot urine protein creatinine ratio is an easy method to estimate the severity of proteinuria. It could be used in between 24 hr collections to roughly estimate the response to therapy.

RENAL FUNCTION :

Serum creatinine is a practical test but as it depends on muscle mass, age and GFR, it is relatively an insensitive early indicator of abnormalities in

GFR.Rather than absolute values it is the change that is important especially significant (20-30% increase).Creatinine clearance is being utilized only rarely since it overestimates the true GFR.

ASSESEMENT OF PROGNOSIS:

There are many demographic and clinical variables which affect the outcome. In general black race,anemia,antiphospolipid syndrome, azotemia, failure to respond to initial therapy and flares with deteriorating renal function are associated with poor outcome.

FACTORS ASSOCIATED WITH ADVERSE PROGNOSIS

DEMOGRAPHIC: Black race, limited access to health care, male sex, children).

CLINICAL: Hypertension; severe extra renal disease affecting major organ; failure to achieve or marked delay (>2 years) to renal remission; multiple flares of lupus nephritis; pregnancy.

LABORATORY: Nephritic urinary sediment, azotemia; anemia; thrombocytopenia; antiphospholipid antibodies; thrombotic microangiopathy; hypocomplementemia (especially falling levels); high anti-DNA (especially rising titers); persistent severe nephrotic syndrome.

HISTOLOGIC: Proliferative glomerulonephritis (WHO class III-IV); mixed

membranous (V) and proliferative (III-IV) glomerulonephritis; cellular crescents; fibrinoid necrosis; very high activity index; moderate-to-high chronicity index; combinations of active (cellular crescents) and chronic histologic features (interstitial fibrosis); extensive subendothelial deposits.

MORBIDITY AND MORTALITY:

Lupus nephritis poses significant morbidity and mortality. In some studies it was found that the health cost of patients with lupus nephritis was twice higher than their fellow lupus patients without it. The major cause of morbidity other than SLE and nephritis include those due to long term corticosteroid use such as infections and osteoporosis.

The five year survival of LN has improved from 17% for class IV LN in 1950s to82% in 1990s. The early mortality was due to sepsis and active SLE while late mortality was due to cardio vascular events and thrombosis. [33].

TREATMENT

Recently European League Against Rheumatism-(EULAR)/ERA-EDTA has published guidelines for treatment of adult and pediatric lupus nephritis[34] wherein the ultimate aims of treatment are preservation of renal function, prevention of disease flares, avoidance of drug related complications, and provision of good quality of life. Treatment must aim for complete renal response.

INDUCTION:

For patients with classIII or class IV(± class V)-MMF 3g/day or low dose IV cyclophosphamide together with steroids.

In patients with poor prognostic features monthly cyclophosphamide can be given (0.75-1 gm/m^2).This should be combined with three pulses of IV methylprednisolone (500-750mg) followed by oral steroids. (0.5mg/kg/day of prednisolone to be given over four weeks and gradually tapered to less than 10 mg /day by six months.

In patients with class V LN who have nephrotic range of proteinuria MMF 3g/day over six months along with steroids is the therapy of choice. As an alternative therapy azathioprine or cyclosporine can also be given in certain patients who do not have poor prognostic features.

MAINTENANCE :

Maintenance therapy is with MMF 2g/day or azathioprine 2mg/kg/day along with low dose steroids. In those patients who were initially treated with MMF it should be continued. If pregnancy is desired azathioprine may be an alternative. In refractory disease treatment can be switched between the drugs.

ADJUNCTIVE TREATMENT [35]

ACE inhibitors in patients with hypertension and proteinuria.

Statins for dylipidemia (target LDL 100 mg%).

Chloroquin for decreasing renal flares and to reduce cardiac and kidney damage.

Aspirin for patients with APS.

Vitamin D and Calcium supplements.

Treatment of comorbidities.

Anti coagulants for patients with nephrotic syndrome (albumin< 2g%) .

LUPUS NEPHRITIS IN PREGNANCY

Pregnancy may be considered if lupus is inactive and Urinary PCR <50 mg/mmol for 6 months, with a GFR > 50 ml/min. Drugs that can be used include hydroxychloroquine,low dose methylprednisolone, azathioprine and calcineurin inhibitors. Treatment intensity should not be reduced in anticipation of pregnancy.

Aspirin should be used to reduce the risk of pre-eclampsia. B.P should be treated with nifedepine or labetolol. Complement levels should be measured to differentiate lupus nephritis flare from preeclampsia.[36, 37]

From the above discussion it is clear that lupus nephritis is characterized by immune complex formation, varied clinical manifestations and multiple laboratory abnormalities with frequent exacerbations. Renal involvement being very common is a major determinant of the disease course. 70-80 % of SLE patients have one or the other form of renal involvement and majority of them present with class IV lupus nephritis. Worldwide survival rates in LN have improved remarkably during successive years due to early diagnosis. Better awareness of risk factors and better treatment modalities also have contributed to this improved prognosis.

Studies done in yester years (in 1970s) by Ester and Christian[38] showed an estimated five year survival rates for patients with lupus nephritis of 50% as against 75% for whole SLE series. The rates for severe kidney disease was even lower,68% for class III and 28% for class IV and V. But in these series patients were being treated only with steroids as immunosuppressants were not widely available at that time. In 1980s and 1990s survival rate became much better around 60-65%.[39 - 41]

As reported by Korbet et al achievement of remission and the type of treatment given also has considerable effect on outcome.[42] The survival rate for patients in his series was 95% at 5 yrs. In this series complete remission was achieved in 43% and time taken to achieve complete remission was 18 months. Stable renal function, lower chronicity index and white race were positive predictors of remission.

A study conducted in Europe by Houssiau & colleagues [43] has reported similar outcomes for patients receiving the conventional NIH Vs ELNT protocol.

According to James Tumlin of Emory university Atlanta [44, 45] poor prognostic factors include persistent anaemia, severity of disease ,time to treatment and duration of remission. In another study in patients treated with intravenous cyclophosphamide an age at diagnosis of < 29 years was associated with a higher risk of progression to LN in 5 years. [46] Also an advanced chronicity index (> 3) at biopsy and a delay to treatment of greater than 5 months were linked to worse outcomes. Patients who did not have a flare-up of their disease had only 25% risk of doubling their serum creatinine in 5 years compared to 75% risk in patients who experienced flare-ups in the observation period.

On the contrary Austin and colleagues, in 1994 reported that , female sex, age > 30 years, black race, the presence of focal necrosis, proteinuria,

crescents,lower C3 (< 76 mg/dL) following therapy and hematocrit of < 26% were associated with a worse prognosis.[47]

Renal biopsy is very important in terms of diagnosis, therapeutics and prognosis. Presence of cellular crescents, interstitial fibrosis was associated with increased risk of progression.[48]

Differences in outcomes of patients with lupus nephritis with and without renal biopsy was studied in a 5 year comparative study by Jakez Ocampo J published in 2004.[49] This study aimed at comparing the 5 year course of patients treated without biopsy with another group with histologic evidence of diffuse proliferative glomerulo nephritis, each group consisting of 30 patients. The no biopsy group had strong clinical and laboratory suspicion of proliferative glomerulonephritis. In this group biopsy was not done either because of medical contraindication or patient's refusal. The biopsy group consisted of patients with histologic diagnosis of diffuse proliferative glomerulonephritis. Patients were regularly followed up from the onset up to 60 months. Results showed that although both groups had deterioration of renal function, no significant differences were found in treatment, outcome, survival, renal function tests or development of renal failure .This study demonstrates that experience in the management of lupus nephritis along with clinical and laboratory data provide enough information to

adequately treat patients with proliferative glomerulonephritis even without renal biopsy.

Studies conducted across the world assessing the outcomes have given varying results. In a study conducted by Senija et al [50] assessing the long term outcome of patients with lupus nephritis, complete remission was achieved in 60.9%, partial remission was accomplished in 29.2% pts during a mean period of follow up of 10.9 yrs.± 4 yrs. This complete remission was sustained for 30.1± 19.1 months and during follow up 29.3% patients developed at least one nephritic flare.

The very long term prognosis of Lupus nephritis was also analyzed by Bono L et al in a study published in Quarterly Journal of Medicine in 1999.[51] In this study 110 patients were analyzed over a median follow up of 15 years. Out of them 40 were dead and 70 alive. Among those alive 38 % had normal renal function and urinalysis. 62% had persistent proteinuria and 18% had decreased but stable renal function. But in this study the predictive power of clinical and histological parameters was not assessed in detail and simple univariate analysis revealed that there was no correlation between any parameters at onset including GFR and survival.

The factors which influence the outcome of ESRD in LN are multifactorial. According to TaK Mao Chan [52] they can be divided into disease related, treatment related, patient and community related and others.

Disease related Extra renal disease activity

Severe irreversible organ damage

Anti Phospholipid Syndrome

Repeated major flares.

Treatment related

Efficacy of immunosuppression

Timeliness of treatment.

Acute and chronic adverse events related to treatment.

Patient and community related

Ethnicity –genetic variations in progression to renal failure

Geographic variations in health care system and economics.

Socio economic factors that affect access to health services and education.

Others: Could be related to disease or to treatment like long term vascular disease.

In a study by Faurschou et al [53] where the authors analyse the outcomes of 91 patients with biopsy proven LN over a median follow up of 6.1 yrs,the cumulative incidence of ESRD after 1,5, and 10 yrs was 3.5%, 15% and 17% respectively. In this study they identified duration of nephritis symptoms greater than six months prior to biopsy as the strongest independent risk factor for ESRD. Others being serum creatinine greater than 140 µmol/L,marked proteinuria, smoking, male sex, higher activity/chronicity index, hypertension, age, race, ethnicity, low response to initial treatment, frequency of flares, socio economic factors, treatment modality, low hemoglobin/hematocrit, thrombocytopenia and histologic features of diffuse proliferative glomerulo nephritis. This study emphasizes the fact that the timing of renal biopsy and treatment are critical factors influencing the prognosis of LN.

Specifically in a recent study published in 2011 in the journal Arthritis Care and Research by Hseih, tubulointerstitial inflammation and not glomerular inflammation predicted progression to renal failure.[54]

Others like Estadile [55]also have shown that early biopsy and treatment is an important prognostic factor. Mortality in LN has reduced compared to earlier decades. Reasons include introduction of immunosuppression in addition to steroids and adjuvant treatment with ACE inhibitors.

The impact of relapses on the final outcome was studied by M El Hachmi Et al. [56] Results published in 2003 concluded that renal relapses are common in patients with lupus nephritis and have a negative impact on outcome but cannot be always predicted. Even years after initial episode regular blood and urine examinations are necessary the importance of which was stressed in this study.

So tight control, frequent monitoring,early diagnosis and treatment are potent ways to improve the outcomes of LN.

The relationship between clinical renal disease and histologic class was analysed in a study by Gladman et al published in Oxford Journal Of medicine in 1989.[57] In this study there was no correlation between clinical disease and renal histology. On the contrary a landmark study by Austin et al [47] discussed the role of clinical and histological data in the prediction of renal outcomes in patients with severe lupus nephritis. The study was conducted in Kidney Disease section, National Institute of Health, Maryland, USA. In this study 65 patients with severe lupus nephritis treated with intravenous cyclophosphamide or methyl prednisolone. Five clinical features were associated with increased risk of doubling of serum creatinine – age more than 30 yrs, black race, hematocrit < 26 %, s.creatine more than 2.4 mgm%, low c3 < 76mg%.After statistical analysis hematocrit, s.creatinine and race were the strongest set of independent clinical predictors of outcome.

Other demographic and clinical features like age and C3 levels did not correlate significantly to outcome prediction when compared to the above mentioned variables. Renal biopsy offered additional information in that patients with severe active and chronic changes on biopsy were at increased risk of developing renal failure. They concluded that outcome prediction based on clinical factors was significantly enhanced by adding pathology data.

The importance of early diagnosis and treatment was also stressed by Fiehn et al in 2003.[58] In this study which compared outcomes during successive decades earlier diagnosis and treatment led to better outcomes.

The correlation between clinical and pathological findings was also studied by Neshad ST and Sepaskhah R at Shiraj medical school, Iran over a period of five years.[59] The study was published in 2008.In this retrospective study 144 patients were analyzed for their clinical features, biopsy class and lab parameters. Edema, hypertension, low serum albumin, increased proteinuria and poor renal function were associated with a worse histologic class .It was concluded that there is a correlation between histologic classification and some of the lab and clinical findings.

Another study from Iran by Ataei N et al[60] in 2008 dealt with outcomes of LN in the Iranian children and the prognostic significance of certain features. The aim of this study was to correlate histopathological features and

outcomes of children with lupus nephritis. In this retrospective study 58 children with biopsy proven LN were followed up between 1989&2005. 58.6% patients had class IV lupus nephritis. The five year survival rate was 82.5% and specifically 75% in class IV lupus nephritis group. The investigators could not detect any independent predictor of poor outcome including renal histology by multivariate analysis.

Reviewing the Indian literature, the long term outcome of lupus nephritis in Indians has been studied by Dhir V et al [61] which analyses the long term outcome of patients studied retrospectively over a period of 20 years at a single center. Here the primary outcome measure was chronic renal failure or death and secondary outcome was end stage renal disease or death. In this study of 188 patients with lupus nephritis, no difference in survival was observed based on histologic class. Risk factors for poor outcome were hematuria, hypertension, creatinine level, low complement, major infection. There was a high rate of infections. It was concluded that with standard immunosuppression the outcome of lupus nephritis in Indians is reasonable.

In a very recent study of eastern Indian patients, short term outcome of 86 cases of proliferative LN was studied .[62] 64% had CR or PR at one year and 14% were treatment refractory. In another study among south Indian patients 82%

of class IV achieved CR in a time of 15 months. [63] In another study of south Indian patients 69% achieved CR or PR at 15.8 months while 31%were refractory. [64]

Among the pediatric patients in India Hari et al [65] from Department of Pediatrics AIIMS, has analyzed the outcome of lupus nephritis in Indian children in a study published in Lupus 2009. This study analysed the clinicopathologic features, treatment and outcome of 54 Indian children. Of the 39 patients who were followed-up 84.6% achieved complete or partial remission, whereas six (15.4%) were refractory to therapy. Three year survival rate was 88% .There was no relation of gender, age of onset, presence of hypertension, haematuria and proteinuria, glomerular filtration rate, renal biopsy and response to therapy to the final outcome of death or ESRD. Patient survival rate was lower compared with the developed countries but similar to developing countries. Serious infections were an important cause of mortality.

In another study published in 2008 from CMC Vellore by Indira Aggarwal et al[66] where 70 children were analyzed for clinical profile, treatment and outcome of SLE, 77.1% had renal involvement and were followed up.The outcomes were defined as i.Remission (normal urinalysis, B.P, s.creatinine, no extra renal symptoms), ii. Active disease (proteinuria >0.5g/day, hypertension, extra renal features, microscopic hematuria >5 RBC's /HPF) , iii) Death and iv) Lost follow up. On follow up for 18.8 months 70 % achieved remission, 7.5 % had

active disease, 7.5% died and 15% lost follow up. There was no correlation between gender, age below 10 years, presence of hypertension, impaired renal function or anemia with renal histopathology. Gross hematuria was significantly associated with more severe renal histopathology. Nephrotic syndrome at presentation had no association with adverse outcomes.

A study analyzing the sex differences in Indian patients with lupus nephritis was published in 2008 by Soni SS et al. [67] This study of 238 patients compared clinical features, lab investigations and histology in males suffering from lupus nephritis with females. The study concluded that renal dysfunction and activity indices were higher in males than females and the difference was statistically significant.

In another study published by Murali et al [68] from CMC vellore, prognosis, survival and life expectancy was analyzed in 98 patients with SLE. Here renal involvement was a poor prognostic factor with proteinuria (>0.5g/day) carrying a 50% reduction in life expectancy. But there was no correlation between disease activity at onset and outcome.

The importance of race as a factor influencing the short term outcome was analyzed in a cohort of 44 patients consisting of African American ethnicity by Lau KK et al in 2006. [69] African American ethnicity has been considered to be a

poor prognostic factor in adult patients with severe lupus nephritis. In this study, consisting predominantly of children of African American ethnicity, 23% achieved complete remission and 48% had partial remission. It was concluded that the clinical presentation and short term outcomes did not differ from the studies with predominantly Caucasians.

From the foregoing discussion it is apparent that studies conducted across the world regarding the association of clinical profile with outcomes in lupus nephritis have given conflicting results. Hence this study was undertaken to analyze the same in patients from our center.

MATERIALS AND METHODS

SETTING Rheumatic Care Center

Rajiv Gandhi Government General Hospital

Madras Medical College

Chennai

STUDY DESIGN :Prospective analytical study

PERIOD OF STUDY Two years from ethical committee approval

ETHICAL COMMITTEE

APPROVAL :Attached

CONSENT :Informed written consent was obtained fro every patient after explaining about the details of the study in their native language.

SELECTION OF SUBJECTS :50 adult cases of new onset lupus nephritis satisfying the inclusion and exclusion criteria

INCLUSION CRITERIA :Adult SLE patients who satisfy the 1997 revised American College of Rheumatology classification criteria [70] with new onset lupus nephritis.

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EXCLUSION CRITERIA :1.Childhood lupus nephritis

2.End stage renal disease

3.Relapsed lupus nephritis

4.Other causes of chronic kidney disease

LIMITATIONS OF THE STUDY

1. Due to technical and financial constraints anti dsDNA antibody, ACL antibody and C3, C4 levels could be measured only in few patients.

2. LAC assay was not done in any patient due to laboratory constraints.

3. Not all patients could be followed up and in one patient outcome could not be assessed.

4. Biopsy was not done in three patients.

5. The study was only a short term outcome study.

6. Activity /chronicity index was available only for a few patients. Hence no attempt at correlating these indices with final outcome was made.

METHODS

Selected demographic, clinical, laboratory and histopathologic data were obtained from the patients and recorded in a proforma (enclosed in annexure).

I. SOCIO DEMOGRAPHIC DATA -Age, sex

II.CLINICAL DATA -Weight, duration , presenting symptoms, extra renal system involved, SLEDAI, BP, co morbidities, time taken to achieve complete remission, duration of follow up.

III. LABORATORY DATA -Hemogram, urinalysis, blood sugar, RFT, LFT,lipid profile, ANA (indirect immunofluorescence method),anti ds DNA (ELISA) , ACL (ELISA), C3 and C4 (radial immunodiffusion).

IV. IMAGING -Ultrasound abdomen was done.

V.HISTOPATHOLOGIC DATA -Renal biopsy was done by percutaneous needle biopsy technique at Department of Nephrology and sent to the pathologist for reporting of classification and analysis by light, electron and immunofluorescent microscopy.

They were treated with one of the following drugs for induction – cyclophosphamide (ELNT or NIH protocol), MMF or azathioprine. They were periodically followed at 3, 6 and 12 months intervals. Outcomes were analyzed at the end of study period.

STATISTICAL METHODS

Statistical analysis was made using SPSS 20 software. Statistical methods used include independent samples test, multi step logistic regression analysis, chi squared test and correlation coefficients. A p value of < 0.05 was considered statistically significant.

DEFINITIONS USED IN THIS STUDY

COMPLETE RESPONSE: Urinary protein/creatinine ratio < 0.5g/24 hrs and normal or near normal GFR (within 10% of normal GFR).

PARTIAL RESPONSE: More than 50% reduction in proteinuria with normal or near normal GFR.

IMPROVED: Any reduction in proteinuria with normalization of GFR.

REFRACTORY: Complete response not achieved by 2 years or partial response not achieved by 6-12 months or improvement not achieved within 3 to 4 months.

FLARE

NEPHRITIC FLARE: Increase in s.creatinine by >30 % or decrease in GFR by >10% and active urinary sediments (RBCs >10 /HPF).

NEPHROTIC FLARE: Doubling of UPCR to more than 1g/day after CR or UPCR to more than 2g/day after PR.

END STAGE RENAL DISEASE: GFR <15 mL/min/1.73 m2, requiring permanent renal replacement therapy (RRT).

GLOMERULAR FILTRATION RATE: As calculated by Cockroft-Gault formula.

{140-age X body weight in kg / 72 X serum creatinine } X 0.85 (if female)

HYPERTENSION: According to the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure (JNC 7)[71] guidelines.

SLEDAI: Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)[72] An objective validated global scale to assess the overall disease activity. It contains 24 items and a total score of 105.

NIH PROTOCOL : Monthly induction pulses of cyclophosphamide at a dose of 0.75- 1gm /m^2 for seven months followed by quarterly pulses for two years beyond remission.

ELNT PROTOCOL: Fixed fortnightly pulses of 500 mg cyclophosphamide (6 pulses) followed by azathioprine or MMF.

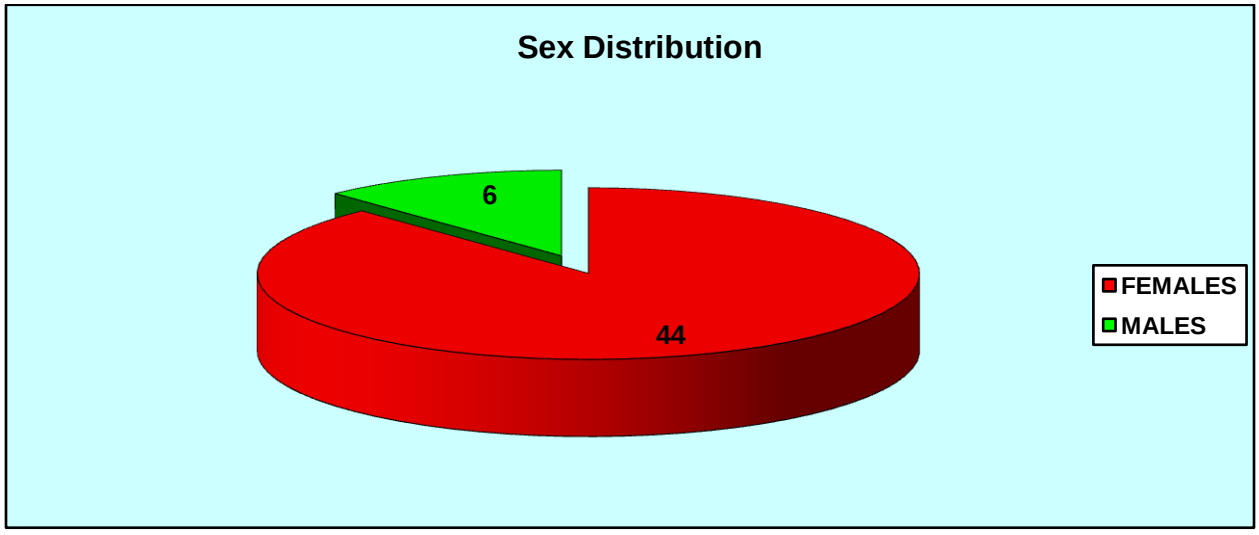
PATIENT PROFILE

A total of 50 patients were enrolled as part of the study and followed up for a period of 2 years (Mean : 17.3 months ;range :1week-24months). Among these forty four were females and six were males. The mean age of the patients was 25.44 years±7.21.The range of age was 16- 47 years.

Table 2

1	NUMBER OF CASES	50
2	FEMALES	44
3.	MALES	6
4.	MEAN AGE	25.44 YRS
5.	STANDARD DEVIATION	7.21

Figure 1



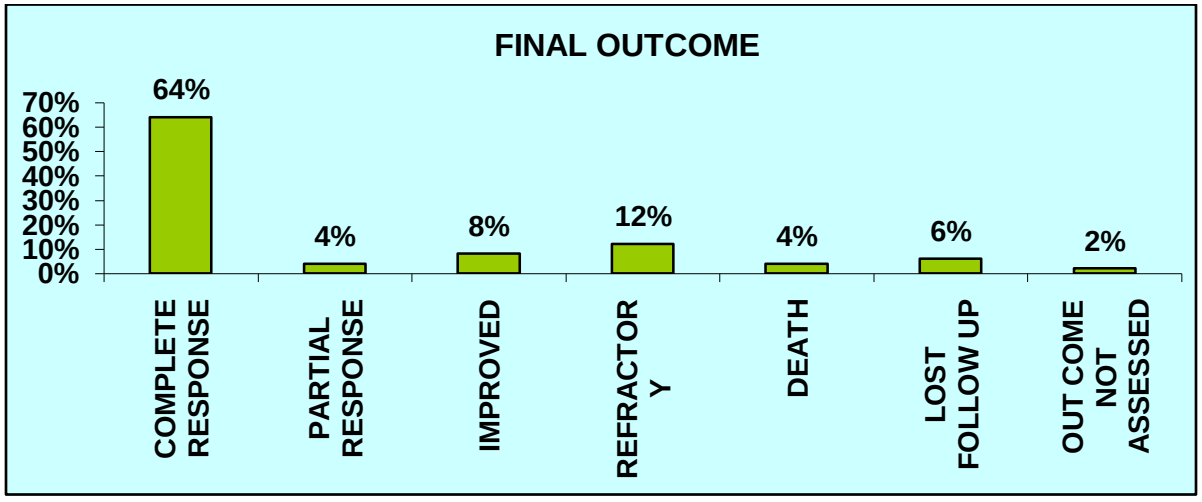
FINAL OUTCOME

The final outcome of these fifty patients were as follows.

Table 3

OUTCOME	NUMBER	PERCENTAGE
COMPLETE RESPONSE	32	64%
PARTIAL RESPONSE	2	4%
IMPROVED	4	8%
REFRACTORY	6	12%
DEATH	2	4%
LOST FOLLOW UP	3	6%
OUT COME NOT ASSESSED	1	2%

Figure 2

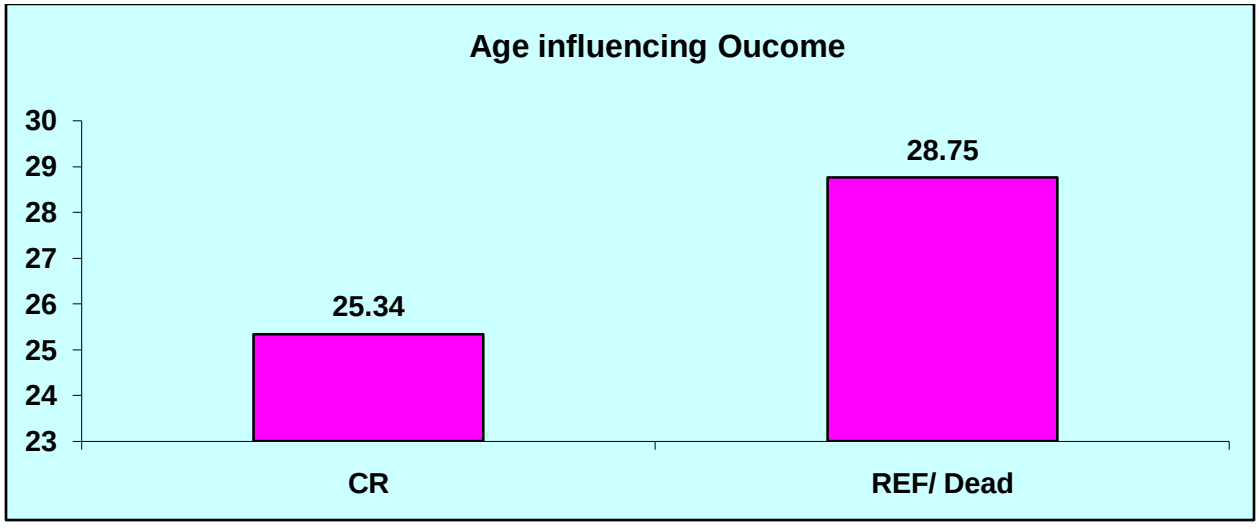


Three patients lost follow up and in one patient the outcome could not be assessed as the patient was not willing for biopsy and was irregular in follow up.

AGE DIFFERENCES IN OUTCOME

The mean age of patients who achieved complete response was 25.34 years (16-47). The mean age of patients who were refractory or dead was 28.75 (range 20-41). On an average, patients who achieved complete response were 3 years younger than those who remained refractory or died. On multistep logistic regression analysis age emerged as an important risk factor influencing the final outcome with p value of 0.047.

Figure 3



GENDER DIFFERENCE IN OUTCOME

Total number of females was 44 and males 6.The mean age of females was 25.27 and 26.67for males (p value for the two samples 0.2529) .

Table 4

	FEMALES	MALES
NO	44	6
MEAN	25.27	26.67
S.D	7.44	4.46

There is no statistically significant difference between the two groups hence both sexes were matched equally for age.

36 (85%) of the females whose outcome was known achieved complete or partial response or improvement. Only (50%) of males achieved CR. By Chi squared test sex was an important factor in determining out come with p value 0.047.

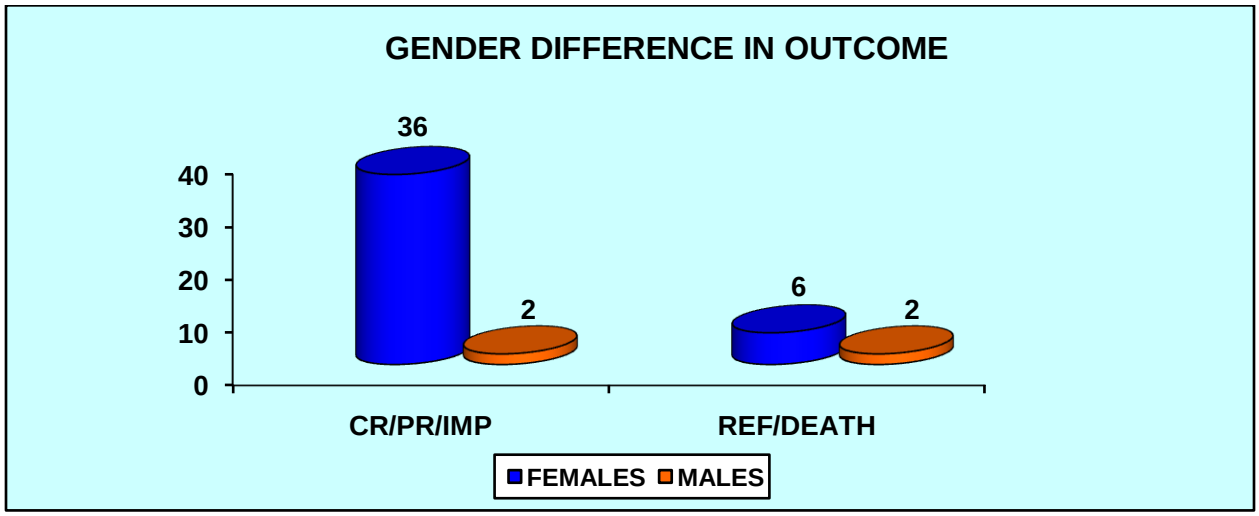
The outcomes according to gender is tabulated below

Table 5

	CR/PR/IMP	REF/DEATH
FEMALE	36	6
MALE	2	2

(Chi square p 0.047 df=1)

Figure 4



DISEASE DURATION

The table below shows the distribution of duration of SLE at the onset of lupus nephritis. The mean duration of illness was 23.3 months. Range 1moths to 84 months. 68% of patients presented within two years.

Table 6

MONTHS	FEMALE	MALE	TOTAL
<12	18	3	21
12—23	5	1	6
24—35	7		7
36—47	5	1	6
48—59	4		4
60—71	1	1	2
72—84	4		4
TOTAL	44	6	50

Mean disease duration in patients who have achieved complete response was 22.81 months while that of the refractory/death group was 33 months[Range 1-84 months in both groups]. Patients who achieved complete response had lesser disease duration of SLE (10.19 months) before the onset of lupus nephritis than the other group. But this difference did not have any effect on the outcome.

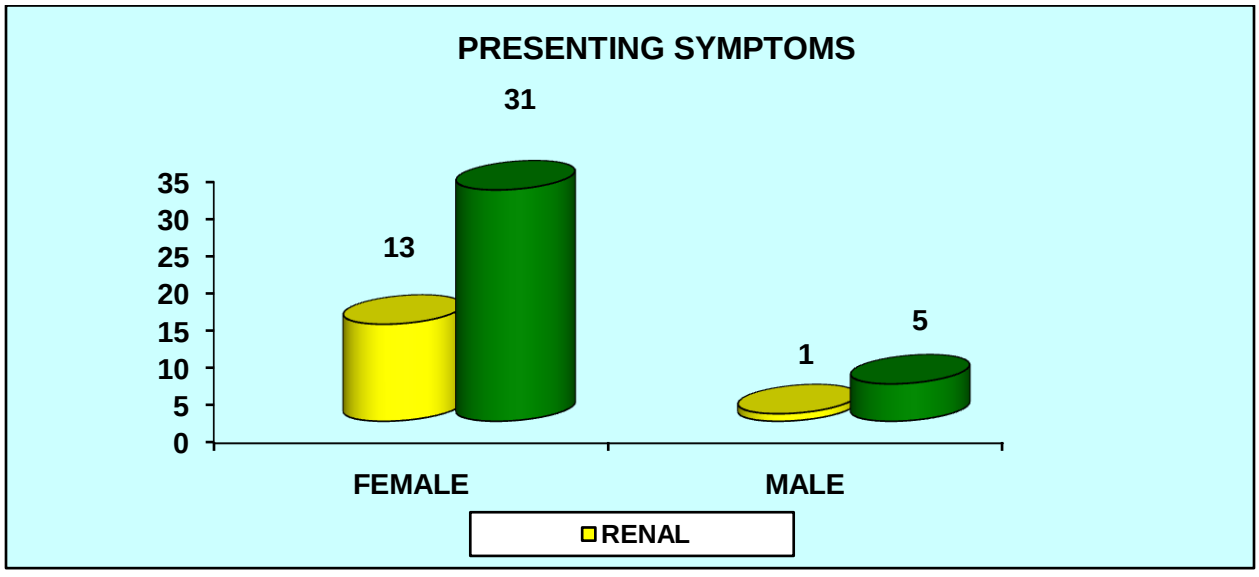
PRESENTING SYMPTOMS

The following was the distribution of presenting symptoms at the onset of lupus nephritis. Only 14 patients (28%) presented with renal symptoms. In others lupus nephritis was asymptomatic and presented with extra renal symptoms.

Table 7

Presentation	FEMALE	MALE	TOTAL
RENAL	13	1	14
EXTRA RENAL	31	5	36
TOTAL			50

Figure 5



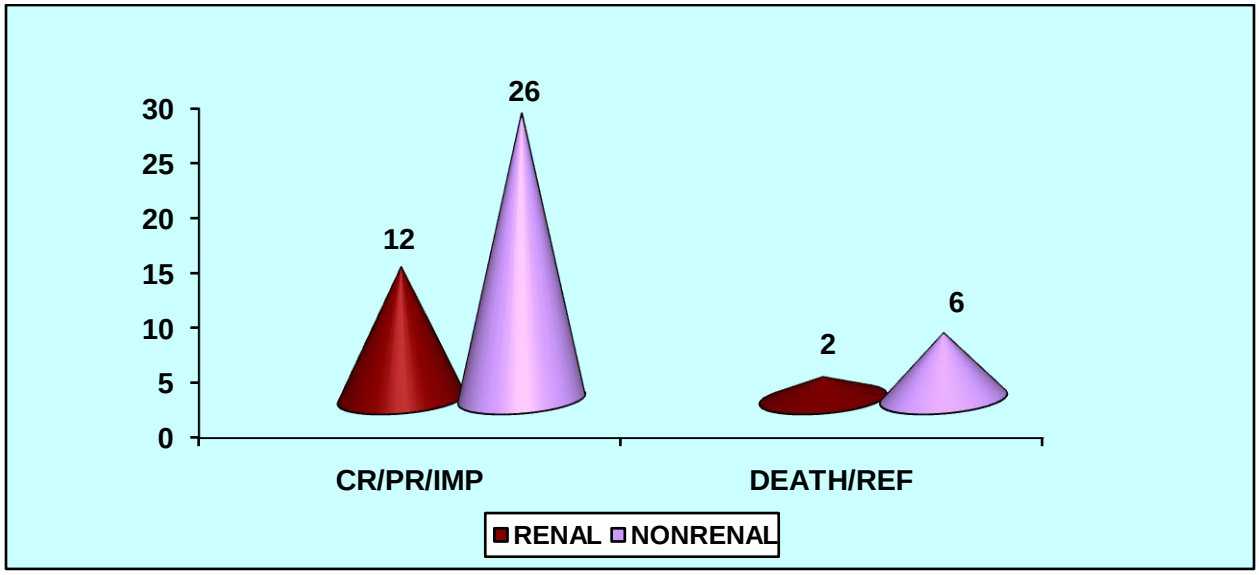
Among those who achieved some response (CR/PR/IMP) 12 presented with renal symptoms and 26 with extra renal symptoms. By Chi square test the presenting symptom did not have any effect on the outcome.

Table 8

	CR/PR/IMP	DEATH/REF
RENAL	12	2
NONRENAL	26	6

(Chi squared test p value 0.71 df =1)

Figure 6



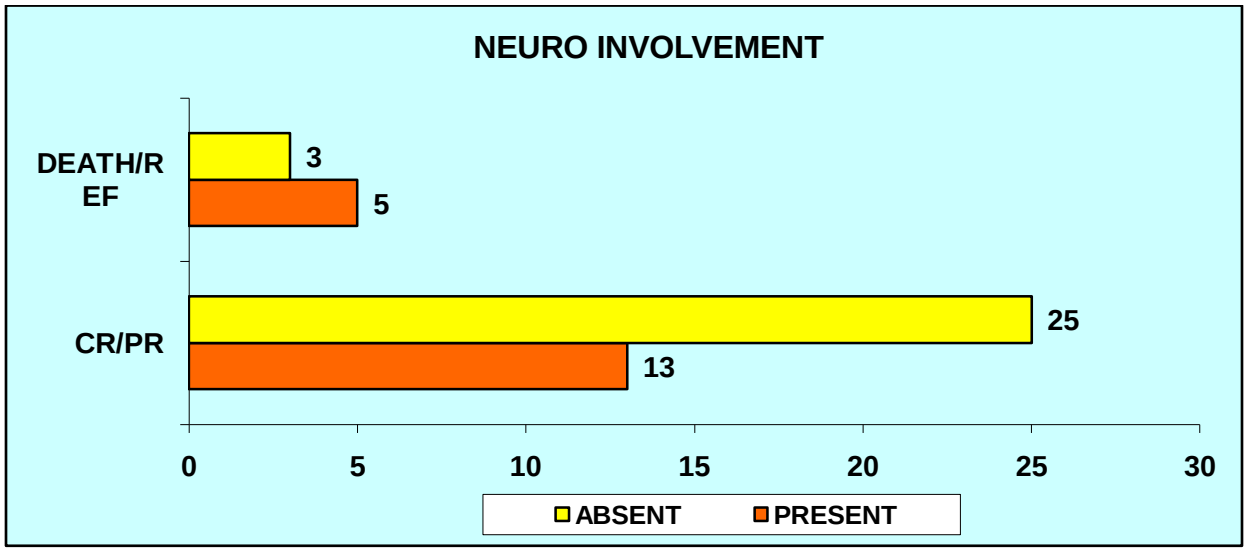
EXTRA RENAL LUPUS

The most common extra renal disease activity affecting the study group was neurologic involvement which was more in patients who were refractory or dead than those who achieved CR/PR though the difference was not statistically significant. Chi squared test p value- 0.27.

Table 9

NEURO INVOLVEMENT	CR/PR	DEATH/REF
PRESENT	13	5
ABSENT	25	3

Figure 7



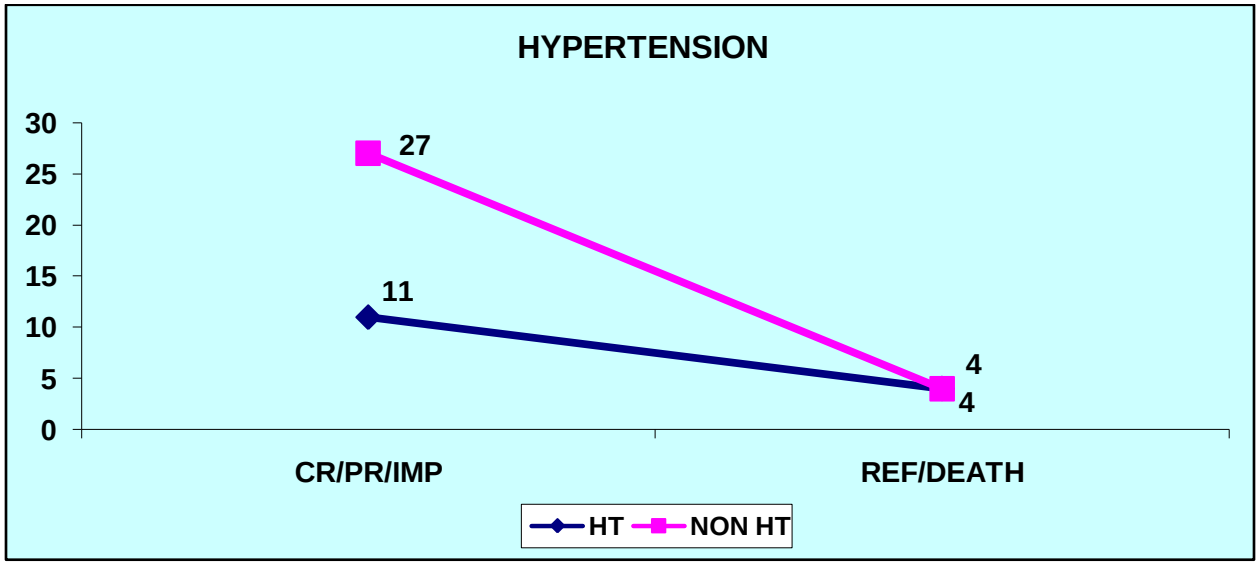
HYPERTENSION

Number of patients with hypertension was 16 (13 females, 3 males). The mean systolic & diastolic BP for CR group was 125.6 & 84 mmHg respectively while that of the refractory/death group was 137.25 & 92.5.Though by Chi squared test there was no significant difference between the group (p Value 0.25).

Table 10

	CR/PR/IMP	REF/DEATH
HT	11	4
NON HT	27	4

Figure 8



COMORBIDITIES

The following were the comorbidities seen.

Table 11

S.No	COMORBIDITY	NUMBERS
1	HYPERTENSION	16
2	HYPOTHYROIDISM	8
3	INFERTILITY	5
4	DIABETES	3
5	PULM.TB	3
6	EXTRA PULM.TB	1
7	OVARIAN TUMOR	2
8	BENIGN ICT	1
9	PREGNANCY	1
10	POST PARTUM	1
11	NEPHROLITHIASIS	1
12	CATARACT	1
13	INFECTIONS	3 (osteomyl-1, skin-1, pneum-1)

The independent samples test comparing the complete response group with the refractory /death group with respect to various clinical parameters is given below. Multistep logistic regression of the variables was also done.

Table 12

INDEPENDENT SAMPLE S TEST				
		t	df	Sig. (2-tailed)
AGE	Assumed	-1.019	38	.314
	not assumed	-1.090	11.778	.297
DURATION	Assumed	-1.054	38	.298
	not assumed	-.842	8.731	.422
SLEDAI	Assumed	-3.132	38	**.003**
	not assumed	-2.304	8.270	**.049**
Hb	Assumed	-.380	38	.706
	not assumed	-.318	9.055	.758
PLATLET	Assumed	.222	38	.825
	not assumed	.232	11.416	.820
S.ALBUMIN	Assumed	.801	38	.428
	not assumed	.802	10.808	.440
S.CREAT	Assumed	-2.727	38	**.010**
	not assumed	-1.891	8.000	**.095**
GFR	Assumed	2.870	38	**.007**
	not assumed	3.433	14.124	.004
ESR	Assumed	.110	38	.913
	not assumed	.120	12.042	.907
URINE PROTEIN	Assumed	-.599	38	.553
	not assumed	-.512	9.198	.621
TIME TO CR	Assumed	-3.449	38	**.001**
	not assumed	-2.077	7.506	.074

Table 13

MULTI STEP LOGISTIC REGRESSION							
		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	AGE	.276	.184	2.259	1	.133	1.318
	DURATIO	.042	.040	1.087	1	.297	1.043
	SLEDAI	.254	.115	4.876	1	.027	1.289
	Hb	.437	.468	.870	1	.351	1.547
	PLATLET	-2.280	2.043	1.246	1	.264	.102
	SALB	1.432	1.462	.959	1	.327	4.185
	CREATI	-1.799	1.704	1.115	1	.291	.165
	GFRI	-.158	.111	2.013	1	.156	.854
	ESR	-.027	.040	.472	1	.492	.973
	ur_INITIAL	.714	.730	.957	1	.328	2.043
	Constant	-7.275	9.531	.583	1	.445	.001
Step 9[a]	AGE	.158	.082	3.686	1	**.047**	1.171
	GFRI	-.064	.025	6.607	1	**.010**	.938
	Constant	-1.902	1.765	1.162	1	.281	.149

a. Variable(s) entered on step 1: AGE, DURATIO, SLEDAI, Hb, PLATLET, SALB, CREATI, GFRI, ESR, ur_INITIAL.

SLEDAI

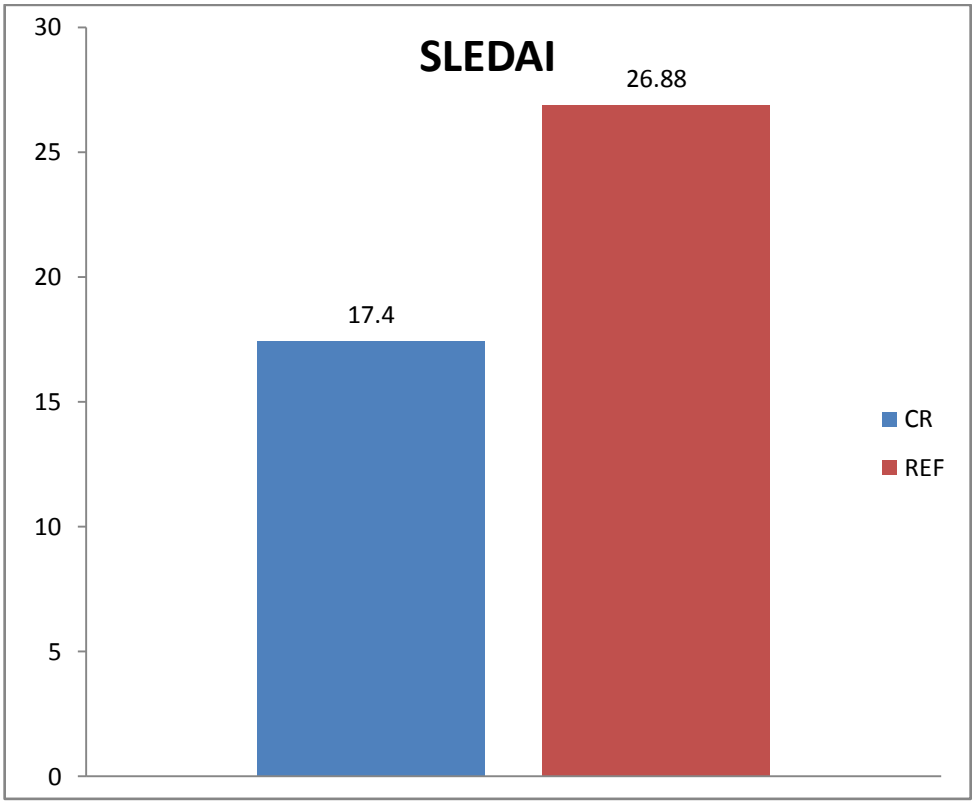
The mean SLEDAI was 19.78 (range 4-45). Mean SLEDAI for females was 18.95 and for males 25.33.

In patients who achieved CR, mean SLEDAI was 17.94 (range 4-30).

In refractory/dead group the mean SLEDAI was 26.88 (16-45).

Using Independent samples test SLEDAI was an important factor defining the outcome [p value 0.003].

Figure 9



HEMOGLOBIN, PLATELET COUNT & SERUM ALBUMIN

The mean hemoglobin of the study group was 8.49 gm% (range 5-13.4).

The mean platelet count of the study group was 1.5lakhs/mm3. No. of patients with platelet count less than 1 lakh was 9 out of 50.

The mean serum albumin value of the study group was 2.83g/dl (range 1.6-3.9).

By independent samples test there was no statistically significant difference between the two groups with respect to hemoglobin, platelet count or serum albumin. Hence these factors did not influence the outcomes in this study.

INITIAL PROTEINURIA:

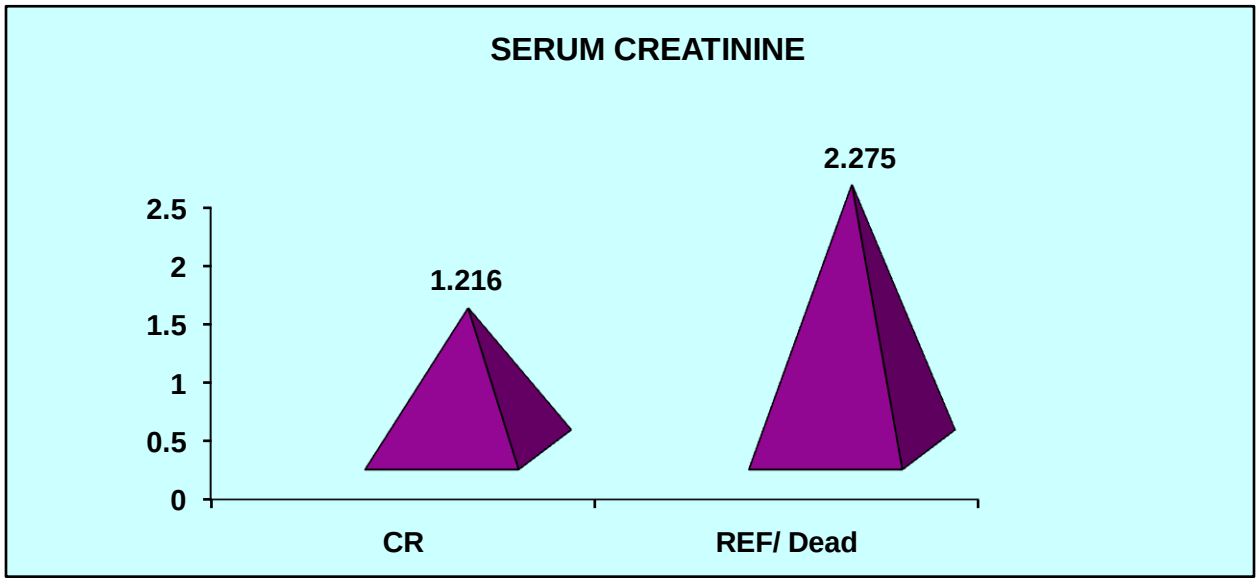
The mean initial proteinuria for the CR group was 2.028 (0.3-5.7) and that of the refractory,dead group was 2.383(0.2-5.2). There was no statistically significant difference between the two groups.

SERUM CREATININE

The mean initial and final serum creatinine of the study group were 1.35 mg% and 0.95 mg% respectively.

The mean initial s.creatinine for the CR group was 1.216 mg% (0.7-3.5) and that of the refractory,dead group was 2.275(range1.0-5). There was a statistically significant difference between the two groups. By independent samples test initial s.creatinine was found to be an important factor influencing the outcome (p value- 0.010).

Figure 10

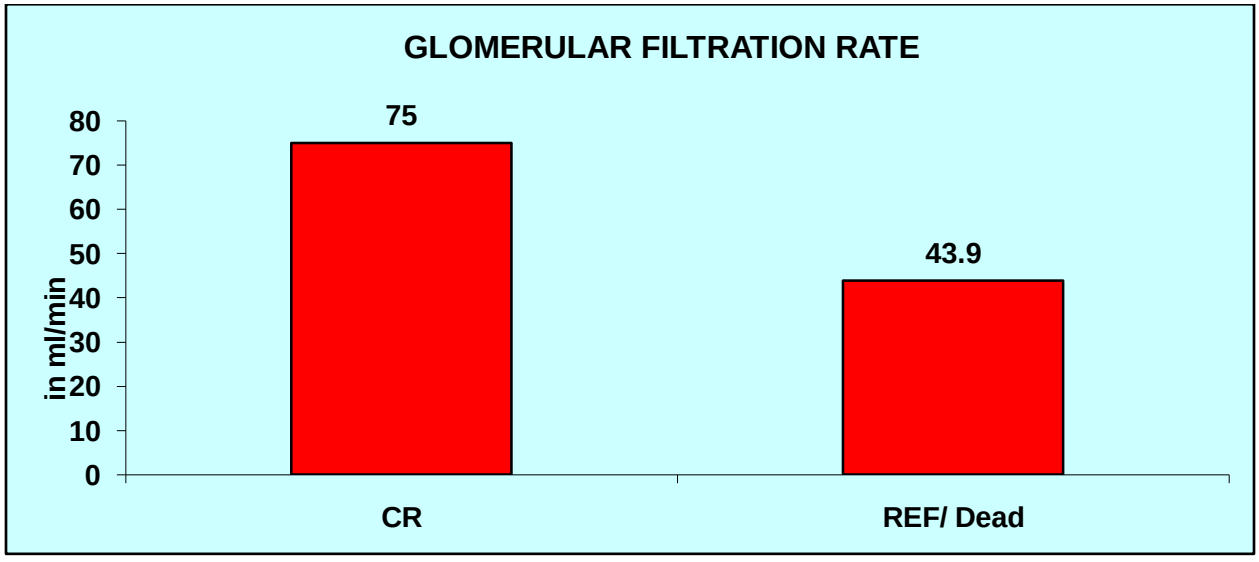


GLOMERULAR FILTRATION RATE

The mean initial and final GFR of the study group were 68.53 ml/min and89.09 ml/min respectively.

The mean initial GFR for the CR group was 75ml/min (16.8-135.8) and that of the refractory /dead group was 43.9 ml/min (14.7-74.4). There was a statistically significant difference between the two groups. By independent samples test initial GFR was found to be an important factor influencing the outcome (p value- 0.007). GFR was also an important factor in determining the outcome in multistep logistic regression (p = 0.01).

Figure 11



TREATMENT PROTOCOLS

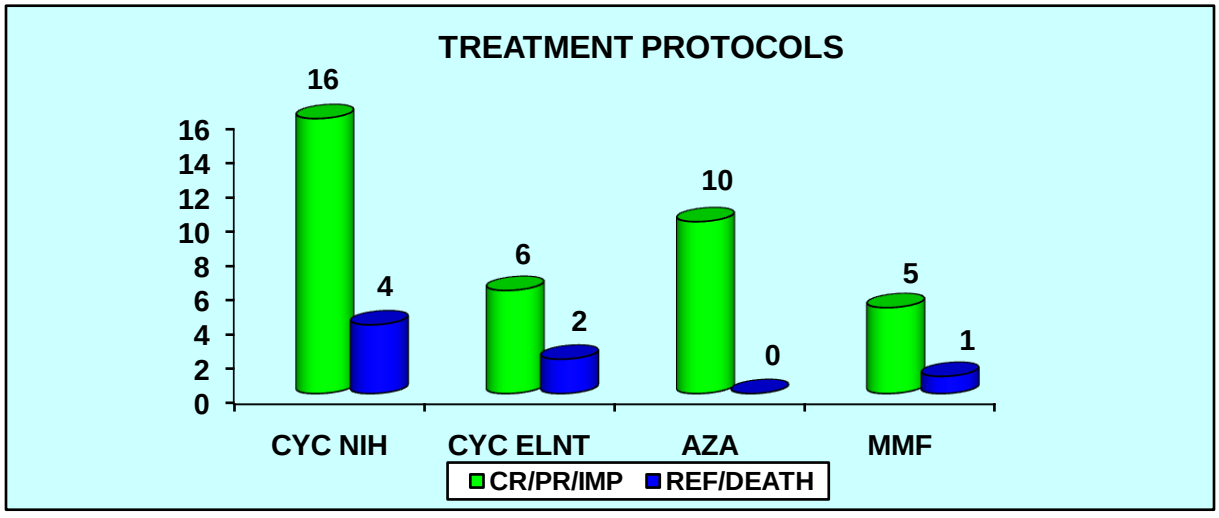
Patients who were treated with cyclophosphamide under NIH or ELNT protocol, azathioprine and MMF achieved 80%, 75%, 100%, 80% response respectively.The treatment protocols used for the induction of treatment did not influence the outcomes.

Table 14

	CR/PR/IMP	REF/DEATH
CYC NIH	16(80%)	4
CYC ELNT	6 (75%)	2
AZA	10 (100%)	0
MMF	5 (80%)	1

Chi squared test ‘p’ value 0.37.

Figure 12



BIOPSY CLASS

Biopsy was not done in 3 patients due to unwillingness. The following is the break up. Class IV was the commonest type (45%) followed by class III (15%) and class II &V (13% each).

Table 15

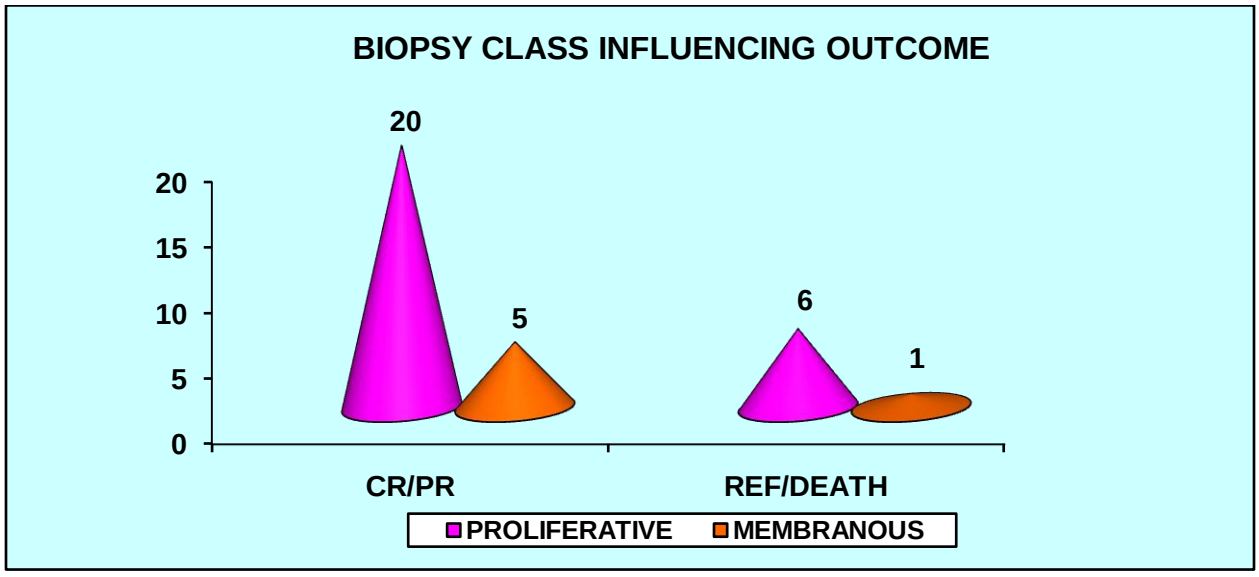
	CR	PR	IMP	REF	DEATH	LOST	TOTAL
CLASS I							
CLASSII	6						6
CLASSIII	4		1	1		1	7
CLASSIV	12	2	1	4	1	1	21
CLASSV	5			1			6
CLASSVI							
CLASSII/V	1		1		1		3
CLASSIII/IV	1						1
CLASSIII/V	1						1
CLASSIV/V			1				1
CLASSIV/VI	1						1

Using Chi squared test there was no significant difference between the outcomes of patients with proliferative type as compared to the membranous type (p value 0.44).

Table 16

BIOPSY CLASS	CR/PR	REF/ DEATH
PROLIFERATIVE	20	6
MEMBRANOUS	5	1

Figure 13



IMMUNOLOGIC PROFILE

All the patients were ANA positive. .Anti ds DNA antibody was done in 29 patients. It was positive in 25 (19 achieved CR/PR/IMP; 4 were refractory or dead,2 LTF). It was negative in 4 (all achieved CR/PR/IMP).

Of those patients for whom antidsDNA antibodies, anticardiolipin antibodies, C3 and C4 were done there was no statistically significant influence on the final outcomes.

Table 17

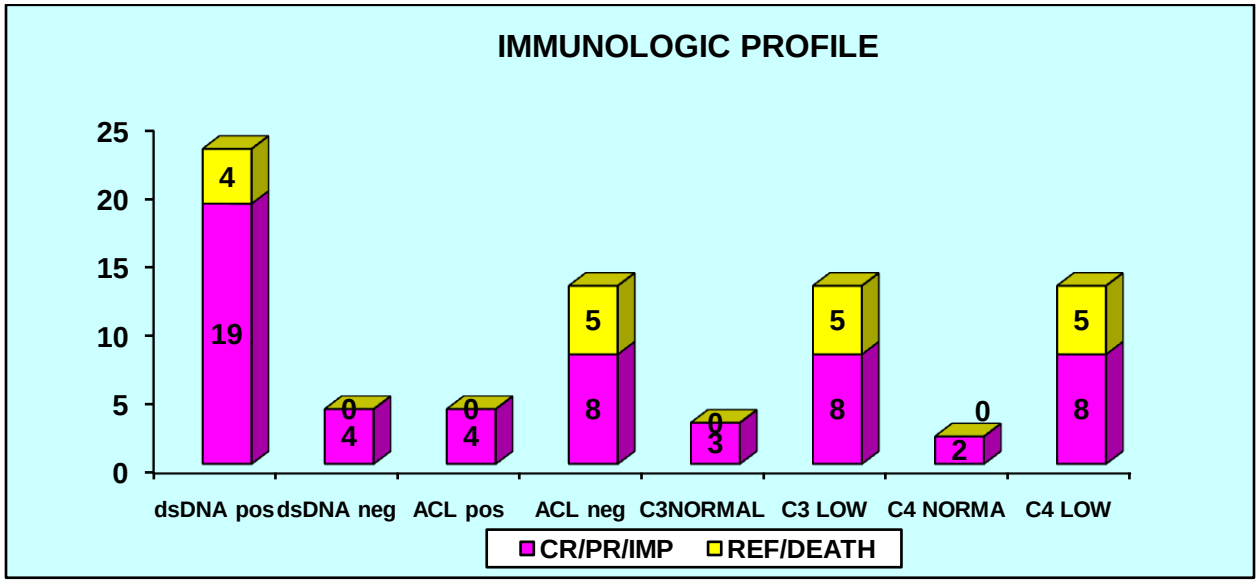
	CR/PR/IMP	REF/DEATH	p value
dsDNA pos	19	4	0.88
dsDNA neg	4	0	
ACL pos	4	0	1.00
ACL neg	8	5	

COMPLEMENT LEVELS AND OUTCOME

Table 18

	CR/PR/IMP	REF/DEATH	p value
C3NORMAL	3	0	0.58
C3 LOW	8	5	
C4NORMAL	2	0	0.52
C4 LOW	8	5	

Figure 14



CORRELATION BETWEEN VARIOUS FACTORS AND COMPLETE RESPONSE

In those patients who achieved complete response the following correlations were made with time taken to achieve complete response.

Table 19

	CORR.COEFF	p VALUE	N value
AGE	0.08	0.85	32
DURATION	-0.02	0.8	32
SLEDAI	0.13	0.4	32
HEMOGLOBIN	-0.02	0.9	32
PLATELET	-0.18	0.25	32
S.ALBUMIN	-0.01	0.9	32
INITIAL CREATININE	0.35	**0.02**	32
GFR INITIAL	-0.13	0.39	32
ESR	0.04	0.798	32
URINE PROTEIN	0.09	0.55	32

Mean time taken to achieve complete response was 9.75 months (range 3-24 months).

AGE : There was small but not significant correlation between age and time taken to complete response (correlation coefficient 0.08).

DURATION OF ILLNESS: There was a negative correlation between duration of illness and time to achieve complete response.

SLEDAI : There was a positive correlation between SLEDAI and time taken to complete response (correlation coefficient +0.132).

There were small negative correlations between hemoglobin level, platelet count and serum albumin (correlation coefficients -0.19,-0.183,-0.01 respectively).

SERUM CREATININE:

There was a strong positive correlation between serum creatinine and time taken to complete response (correlation coefficient +0.353, p value 0.026). Hence higher the creatinine value longer was the time taken to achieve complete response.

GFR levels had a negative correlation with time taken to complete response (correlation coefficient -0.138) and initial urine protein levels had a small positive correlation (correlation coefficient +0.09).

DISCUSSION

Lupus nephritis is one of the major manifestations determining the course of illness in patients with SLE. A number of studies have found a good correlation between clinical data and outcomes in LN while others have not.

In the present study the outcome of complete response was achieved in 32 patients (64%), partial response in 2 patients (4%) and improvement in 4 patients (8%). Six patients (12%) were refractory to treatment; 2 patients died (4%); follow up was lost in 3 patients and in one patient the final outcome could not be assessed.

The percentage of patients who achieved complete response was similar to the study by Senija et al. [50]But this was a long term study with average follow up period of 10.9 years. In a short term Indian study 64% achieved CR or PR at one year. [62] In another study [42] CR was achieved in 43% with mean time taken to achieve CR was 18 months whereas in our study the time taken to achieve CR was 9.75 months .The time taken to achieve CR was 4.5 ±1.9 months in the above mentioned Indian study.

The differences in outcome and time taken to achieve CR could be explained by racial and genetic differences to therapy. A study published in India has concluded that if standard immunosupression is given the outcome of LN is

reasonably good.[61] Studies published in India among pediatric patients have also supported this notion. In a study from AIIMS [65] 84.6 % achieved complete or partial response in one year and 15.4% were refractory. In another study from CMC Vellore [66] 70% achieved remission in 18.8 months and 7.5 % died.

Average age of patients who achieved CR was 3 years lower than (statistically significant) those who remained refractory or dead . Previous study by Austin [47]and collegues concluded that age more than 30 years is associated with worse outcome. On the contrary in another study [44] age less than 29 years was associated with poor outcome. Higher age may be associated with poor renal function, decreased serum albumin, increased ESR and proteinuria and comorbidities like hypertension and diabetes .

The importance of sex as a prognostic factor influencing the outcome has been studied before. [47] In one study female sex was associated with worse prognosis while in another study by Faurschou M [53] male sex was associated with poor prognosis. In India a study by Soni et al [67]found statistically significant difference between male and female patients with LN with regards to renal function and activity index (poorer in males). In our study also there was a statistically significant difference between males and females in achieving complete or partial response with males faring poorly. The reason may be due to males having higher disease activity.[73]

As acknowledged world wide [62] majority of the patients in our study (72%) did not present with symptoms pertaining to renal involvement. LN was diagnosed during routine investigations. But this factor did not influence the final outcome as almost all patients with abnormal urine examination underwent renal biopsy in our set up regardless of their presenting symptoms.

Major extra renal disease activity affecting the outcome was neurologic involvement and was seen in 40 % of patients. Neurologic involvement was more in patients who were refractory or dead though the value was not statistically significant.

Primary infertility, problems with pregnancy and post partum state, ovarian tumors were seen in 9 female patients. As seen in other Indian studies [61, 62] the most common complication of therapy was infections (14%) . These along with socioeconomic constraints hampered the therapeutic decision making as typical of any developing country.

The mean SLEDAI of patients achieving CR was lower than that of patients who remained refractory or died (statistically significant). Also higher SLEDAI correlated positively with delay in achieving remission. This result was similar to that of a study by James Tumlin [44] whereas in the study by Sircar et al [62] there was no significant correlation between SLEDAI and outcomes.

There was no statistically significant difference between the mean hemoglobin level between the two groups in contrast to some studies. [53] This could be explained by the fact that anemia is grossly prevalent in Indian women (51%) [74] hence it is not surprising that women with SLE and LN are anemic. But using correlation coefficient patients with low hemoglobin were found to take longer time to achieve complete response. Similar results were seen with low platelet counts and serum albumin, high ESR and initial proteinuria.

An important observation made was that more number of patients in CR/PR group (27) were normotensive while 11 had hypertension though this did not affect the final outcome.

As seen in earlier studies [42, 53, 61] higher initial serum creatinine and lower GFR were poor prognostic factors influencing the outcomes (statistically significant difference between the two groups). Also high serum creatinine at onset of illness significantly affected the time taken to achieve complete response. Initial GFR value also correlated negatively with time taken to achieve CR though in some studies there is no correlation between outcomes and GFR. [62]

There was no significant association between anti ds DNA and ACL antibody positivity and hypocomplementemia and the outcomes. But as mentioned

earlier they were done only in few patients due to technical and financial constraints which could have skewed the results.

Analysing the treatment protocols used for induction treatment 75-80% of those patients who were started on MMF/ cyclophosphamide under ELNT or NIH protocol achieved CR/PR or improved. Under the recent guidelines issued by EULAR/ERA-EDTA [34], MMF has emerged as the treatment modality of choice in patients with class III/IV/V LN due to favorable toxicity profile. 11 of 16 (69%) patients who achieved response under NIH protocol belonged to class IV and 4 of 6 (66%) patients who achieved response under ELNT protocol belonged to class IV.

So in our set up cyclophosphamide under ELNT or NIH protocol are equally effective in class IV LN. When ELNT protocol was originally initiated in young European women with LN who did not have adverse prognostic factors, it was thought that it might not be suitable for patients of other races with poor prognostic features. But 10 years down the lane recently long term results of ELNT have been published which show that outcomes like ESRD and death did not differ much in patients treated under this protocol from those who received conventional treatment.[75]

In this study apparently all the ten patients who received azathioprine as induction treatment achieved CR/PR or improved while none was refractory. This may be quiet surprising in the context of recent findings which have shown that patients initiated on azathioprine as induction treatment for proliferative LN have produced poorer outcomes. But on close analysis it can be found that 50% of our patients started on azathioprine belonged to class II (all achieved CR), where it was used as a steroid sparing agent. In one patient biopsy was not done and with all probability that she may belong to class II, she was treated on clinical grounds. While one patient improved and another achieved only partial response, 2 patients each belonging to class IV and V achieved CR.

Analyzing the histologic class, as seen in other parts of the country class IV LN is the commonest histologic class seen in this study. Previous studies regarding the role of histologic class influencing the outcome of nephritis have been controversial. In the study by Faurschou et al [53]diffuse proliferative glomerulo nephritis strongly correlated with the outcome of ESRD while in Indians in a study by Dhir et al[61] no difference in survival based on histologic class was found. Among Indian children also there are studies which showed no correlation between histologic class and end results like ESRD/ death. In this study also there was no relation to outcome and histologic class.

Among patients who achieved CR, four patients (12.5%) flared-3 patients had nephritic flare and one patient had proteinuric flare. This is slightly higher than that observed in an Indian study (7.7%).[62] In one of these patients (a female patient of class IV LN) the dose of immunosuppression was increased and the patient continued to be in CR. In another patient repeat biopsy showed a class switch from IV to VI. He rapidly progressed to ESRD, had persistent extra renal activity and died. The second patient who died even before treatment could be initiated was a female, of class II/V LN and had severe extra renal activity. The third patient (class II LN) with nephritic flare was being planned for repeat biopsy at the time of completion of study. In one female patient with proteinuric flare, the maintenance immunosuppression was changed from azathioprine to MMF and the patient continues to be in CR.

One patient who achieved CR at 6 months lost follow up there after. One patient who was initially refractory to MMF responded to cyclophosphamide after repeat biopsy showed the same class (classIV) and she achieved CR at the end of the study period.In those patients who remain refractory at the end of the study period treatment decisions have been hampered by socio economic conditions like presence of pregnancy, desire to conceive and the cost of alternative therapy.

CONCLUSION

1. Among fifty patients 64% achieved complete response,4% achieved partial response , 8% improved while 12% remained refractory and 4% died.

2. Lower age, female sex, lower disease activity, good initial renal function (low s.creatinine, high initial eGFRwere important factors associated with favourable outcome.

3. Presenting symptoms, disease duration, extra renal disease activity, presence of hypertension, haemoglobin, platelet counts, serum albumin levels, treatment protocols and biopsy class did not significantly influence the outcome.

4. Among patients who achieved complete response initial serum creatinine positively correlated with time taken for outcome (statistically significant).

5. Higher age, disease activity, ESR and initial proteinuria positively correlated with time taken to complete response (not statistically significant).

6. Hemoglobin, platelet count, albumin, GFR showed negative correlation with time to complete response (not statistically significant).

7. In south Indian patients long term studies are needed to analyze the correlation between clinical features and outcomes in lupus nephritis.

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MASTER CHART

											INITIAL		FINAL			URINE	PROTEIN	TRAETMENT		FINAL		
S.No	RCC	AGE	SEX	DURATION	SLEDAI	Hb	PLATELET	SYS.BP	DIAS BP	ALBUMIN	CREAT	GFR I	CREAT	GFR II	BIOPSY	INITIAL	FINAL	INDUCT	MAINT	OUTCOME	FOLLOW UP	TIME TO CR
1	53467	27	F	12	45	5.9	2	180	120	1.6	1.2	55.58	1.3	55.3	classIV	1.86	1.56	CYC(elnt)	AZA	REF	24	
2	54129	29	F	84	27	8.8	1.89	140	90	2.7	2	31			classV/II	5.2				DEATH	0.25	
3	54495	21	F	72	17	9.1	1.72	100	70	3.7	0.9	109.7	0.8	120	classIV	2.4	0.4	CYC NIH		CR	24	6
4	54083	24	F	6	9	9	1	120	80	3.4	1.2	50.21			classIV	3.7		CYC(elnt)	AZA	LOST	2	
5	54112	29	F	3	7	10.2	1.68	110	80	2.8	1.1	59.6	0.8	81.9	classIII	2	0.03	AZA	AZA	CR	22	6
6	54576	28	F	36	25	9.8	2.1	120	80	3.2	0.8	82.6	0.8	82.6	classIII/IV	4.3	0.08	CYC NIH		CR	18	6
7	54297	22	F	12	25	6.3	0.95	100	70	3.2	1	83.58	1	89.2	classIV	2.6	0.4	CYC NIH	AZA	CR	20	12
8	54056	25	F	2	29	9.3	1.75	120	80	3.7	2.2	30.2	0.7	107	classII	0.28	0.08	AZA	AZA	CR	24	6
9	52987	38	F	24	9	11	1.93	120	80	3.9	0.7	89.5	0.7	89.5	classII	0.3	0.05	AZA	AZA	CR	24	6
10	54182	16	F	2	11	10.6	2.18	110	80	1.8	1	67.35	0.8	84.2	classIII	2.6	0.05	CYC(elnt)	AZA	CR	22	6
11	55650	30	F	7	15	6	0.67	150	110	3.4	1.4	51.2	0.7	107.6	classIV	0.7	0.08	CYC NIH		CR	3	3
12	46585	20	F	48	14	5	2.35	110	60	2.1	1.2	53.1	0.8	70	classIII/V	0.8	0.03	CYC(elnt)	AZA	CR	24	6
13	50098	18	F	36	18	5.2	0.8	150	110	2	3.5	18	0.8	99.02	classIV	3.5	0.2	CYC (elent	MMF	CR	24	12
14	46094	41	F	72	12	10.6	1.6	120	80	2.2	1.1	74.38	1.4	61.38	classIV	2.5	2.3	MMF		REF	24	
15	54623	26	F	5	11	9.8	1.62	90	60	3.5	1	67.3	1.2	60.22	classIII	0.75	0.75	CYC NIH	AZA	REF	13	
16	50329	30	M	60	14	7	2.5	160	110	3.7	0.9	135.8	1	128.33	classIV	3.95	0.03	CYC NIH		CR	24	24
17	51487	20	F	24	19	9.8	1.62	110	70	3.8	0.7	101	0.7	109	classIII	2.7	0.35	MMF		CR	24	12
18	55432	19	F	36	26	5	1.62	150	110	2.3	3.4	16.81	0.7	89.79	classIV	0.5	0.07	CYC NIH		CR	24	12
19	55860	22	F	12	38	9.8	1.7	130	80	1.8	3.3	27.3	1.3	75	classIV/VI	0.67	0.2	CYC /NIH		CR	24	6
20	49810	37	F	48	12	9.4	1.78	160	100	3.2	0.9	94.58	0.9	99.9	classII	0.7	0.3	AZA	AZA	CR	24	6
21	53456	17	F	12	21	10.2	1.76	110	70	3.5	1.1	52.8	0.8	79.6	classIV	1.5	0.03	CYC(elnt)	AZA	CR	18	6
22	55096	19	F	2	19	10.2	1.82	120	70	3.2	0.9	63.49	0.8	80.35	classIII	0.5	0.05	CYC NIH		CR	12	6
23	55123	19	F	24	23	6.9	1.52	110	80	2	0.8	73.21	0.7	87.75	classV	2.1	0.3	MMF	MMF	CR	12	12
24	53976	24	F	18	6	6.2	0.88	120	80	3.4	0.8	85.8	0.8	116.7	classIV	4	3.1	MMF		IMP	4	
25	55705	23	F	3	19	7	1.52	120	90	2.7	1.2	57			not done	5.4		AZA	AZA	LOST	2	
26	54104	23	F	24	17	9.8	1.75	110	70	2.4	1	69.2	0.8	93.23	classIV	3.3	1.6	AZA	AZA	PR	18	
27	55360	24	F	6	25	9	1.15	110	80	2.2	0.8	77.03	0.8	85.89	classV	5.7	0.4	CYC NIH		CR	10	6
28	54615	23	M	4	23	9.7	2.58	120	70	2.7	0.9	124	0.8	120.8	classIV	1.6	0.07	CYC NIH		CR	18	6
29	55930	18	F	1	20	10.8	0.9	120	80	2.5	0.7	72.1	0.7	78.9	classIII	1.21	1	MMF		IMP	3	
30	54883	24	M	12	29	8.6	1.4	170	110	1.4	1.1	96.7			not done	1.9		CYC NIH		CANT BE ASSESD	13	
31	53104	26	M	36	25	13.4	1.85	150	100	2.2	3.9	21	3.6	26.3	classIV	3.75	3	CYC NIH		REF	24	
32	53199	34	M	4	39	6.6	1.8	100	70	2.5	5	14.72			classIV	0.2		CYC NIH		DEATH	24	
33	49876	19	F	84	14	5.5	1.45	150	100	3.5	1.5	55.4	0.9	101.5	classIV	1.4	0.04	CYC(elnt)	AZA	CR	24	6
34	48248	26	F	36	12	9.8	1.64	120	80	2.8	1.1	80.4	1	99.59	classV	1.5	0.07	CYC NIH		CR	24	6
35	47628	20	F	48	28	7.1	1.65	190	120	3.4	1.5	45.33	1.6	44.27	classIV	0.7	0.6	CYC (eint)	MMF	REF	24	
36	53476	47	F	24	20	9	1.4	150	100	2.4	0.7	100.3	0.6	124.5	classII	0.6	nil	AZA	AZA	CR	15	12
37	55306	27	F	5	4	5.5	1.02	120	80	3.5	0.8	96.75	0.8	103.6	classIV	2.5	0.07	CYC NIH	AZA	LOST	18	
38	51641	41	F	7	12	10.2	1.49	170	100	3	1.5	54.4	1	86.49	classIV/V	4	3.1	CYC NIH		IMP	3	
39	55723	18	F	36	16	8.2	1.4	100	70	3	1.6	39.1	1	69.13	classII/V	2	1.5	AZA		IMP	3	
40	54738	36	F	24	24	8.5	1.8	110	80	2.1	0.9	76.14	0.8	92.8	classII	1.06	0.04	AZA		CR	24	12
41	48934	30	F	24	22	6.6	2.98	120	80	2.8	1.1	66.1	0.7	111.3	classIV	3.3	0.03	CYC NIH		CR	24	12
42	46800	20	F	1	25	6.8	1.5	150	100	2.5	0.9	100.74	0.8	116.8	classII/V	2.95	0.03	MMF		CR	24	12

											INITIAL		FINAL			URINE	PROTEIN	TRAETMENT		FINAL		
S.No	RCC	AGE	SEX	DURATION	SLEDAI	Hb	PLATELET	SYS.BP	DIAS BP	ALBUMIN	CREAT	GFR I	CREAT	GFR II	BIOPSY	INITIAL	FINAL	INDUCT	MAINT	OUTCOME	FOLLOW UP	TIME TO CR
43	55940	21	F	4	23	7.9	1.8	100	70	3.5	0.9	62.44	0.7	88.31	not done	0.8	0.08	AZA		CR	3	3
44	53486	24	F	1	35	8.7	0.9	120	80	2.5	0.8	99.28	0.7	106.82	classV	2.5	0.18	CYC NIH		CR	24	24
45	54486	38	F	3	11	9.3	1.6	110	80	3.5	0.7	99.77	0.7	110.1	classV	2.6	0.02	AZA		CR	24	24
46	47856	23	F	3	16	7	0.4	130	100	3.3	2.1	42.1	1.8	50.65	classV	4.1	2	CYC NIH	AZA	REF	24	
47	55654	23	M	4	25	9	0.9	110	70	2.5	0.9	83.67			classII	2.7		AZA		LOST	2	
48	47997	25	F	48	14	9.8	1.86	180	120	1.8	1.1	67.88	1.1	70	classIV	1.3	0.15	CYC NIH		CR	24	18
49	55647	21	F	6	20	10.2	0.62	120	80	3.4	0.9	84.29	0.8	101.85	classII	5	0.12	LOW STEROID		CR	17	6
50	46787	17	F	60	19	9.8	2	120	80	3.5	0.8	72.6	0.7	95.42	classIV	1.5	0.6	CYC ELNT	AZA	PR	18	

Age-Years, Duration- Months, Hb- grams%, Platelet- L cumm, BP-mmHg, Albumin- gm%, Creatining- mg%, GFR-ml/min, Proteinuria-gm/day, Followup, time to CR- Months

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No : 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr.S.Vidya ,
PG in DM Rheumatology,
Madras Medical College, Chennai -3

Dear Dr.S.Vidya,

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled " A study on the association of clinical profile with the outcomes of Lupus Nephritis No.21022011.

The following members of Ethics Committee were present in the meeting held on 17.02.2011 conducted at Madras Medical College, Chennai -3.

1. Prof. S.K.Rajan, MD	-- Chairperson
2. Prof. A.Sundaram, MD Dean i/c, Madras Medical College, Ch-3	-- Member Secretary
3. Prof. Sathianathan Director Institute of Psychiatry , MMC, Ch-3	-- Member
4. Prof. R.Nandhini, MD Director, Instt. of Pharmacology, MMC, Ch-3	-- Member
5. Prof. Pregna B. Dolia MD Director, Institute of Biochemistry, MMC, Ch-3	-- Member
6. Prof. C.Rajendran, MD Director, Institute of Internal Medicine, MMC, Ch-3	-- Member
7. Prof. Geetha Subramanian, MD, DM Por. & Head, Dept. of Cardiology, MMC, Ch-3	--- Member
8. Thiru.A.Ulaganathan Administrative Officer, MMC, Ch-3	--- Layperson
9. Thiru.S.Govindasamy, BA. BL	--- Lawyer
10. Tmt, Arnold Saulina	--- 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.

Sd/- Dr.A.Sundaram, Vice Principal
Member Secretary, Ethics Committee

True copy
R Nandini 21/2/13
Vice Principal
21/2/13

A STUDY ON THE ASSOCIATION OF CLINICAL PROFILE WITH THE OUTCOMES OF LUPUS NEPHRITIS

Name: Age: Sex: Date:

RCC No.

H/o. Present Illness:

Past History:

Family History:

Personal History:

Treatment History:

General Examination

Pallor: Icterus Cyanosis

Clubbing: Lymphadenopathy: Pedal Edema:

Skin:

Nails:

Hair:

Pulse BP

Systemic Examination

Cardio vascular system- Respiratory system-

Abdomen- Central nervous system-

Musculoskeletal System Examination:

SLEDAI

INVESTIGATION

Haemogram

Hb:	TC:	DC:
Platelet:	ESR:	

Immunological

CRP:	ANA:

Biochemical

Blood

Sugar:	Urea:	Creatinine:
Bilirubin:	AST:	ALT:
ALP:	Total Proteins:	Albumin:
Lipid profile	CPK	LDH

Urine analysis

Radiography

1.X-Rays

2. Ultra sound abdomen KUB

Renal Biopsy

PATIENT CONSENT FORM

Study Details : "A study on the association of clinical profile with the out comes in Lupus nephritis"

Study Centre : Department of Rheumatology, Madras Medical College, Chennai.

Patient may check (√) these boxes

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask questions and all my questions and doubts have been answered to my complete satisfaction. ☐

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

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ☐

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

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

I hereby consent to participate in this study ☐

Signature/ Thumb Impression:

Patient's Name and Address: **Place** **Date**

Signature of Investigator

Study Investigator's Name: Place Date

ஆராய்ச்சி ஒப்புதல் கடிதம்

ஆராய்ச்சி தலைப்பு

மண்டலீய செங்கரடு (SLE) நோயாளிகளுக்கு ஏற்படும் சிறுநீரக அழற்சி நோய்

பெயர்	:	தேதி	:
வயது	:	உள்நோயாளி எண்	:
பால்	:	ஆராய்ச்சி சேர்க்கை எண்	:

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கம் முழுமையாக எனக்கு தெளிவாக விளக்கப்பட்டது.

எனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்து கொண்டு நான் எனது சம்மதத்தை தருகிறேன். மற்றும் ஆராய்ச்சியில் பங்கேற்க நான் சம்மதம் தெரிவிக்கிறேன்.

இந்த ஆராய்ச்சியில் பிறரின் நிர்ப்பந்தமின்றி என் சொந்த விருப்பத்தின் பேரில் நான் பங்கு பெறுகிறேன் மற்றும் நான் இந்த ஆராய்ச்சியிலிருந்து எந்நேரமும் பின்வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்து கொண்டேன்.

நான் என்னுடைய சுயநினைவுடன் மற்றும் முழு சுதந்திரத்துடன் இந்த மருத்துவ ஆராய்ச்சியில் என்னை சேர்த்துக் கொள்ள சம்மதிக்கிறேன்.

கையொப்பம்

INFORMATION SHEET

We are conducting at A study on the association of clinical profile with the outcomes in Lupus nephritis at The Department of Rheumatology, Madras Medical College, Chennai.

The purpose of the study is to find out the association clinical profile with the out comes in Lupus nephritis

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 results 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 *Signature of participant*

Date:

ஆராய்ச்சி தகவல் தாள்

சென்னை அரசு பொது மருத்துவமனையில் "மண்டலீய செங்கரடு (SLE) நோயாளிகளுக்கு ஏற்படும் சிறுநீரக அழற்சி நோய்" பற்றிய ஆராய்சி நடைபெறுகிறது.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். இந்த ஆராய்ச்சியில் பங்கேற்பதால் தங்களது நோயின் ஆய்வறிக்கையோ அல்லது சிகிச்சையோ பாதிப்புக்கு உள்ளாகாது என்பதையும் தெரிவித்துக் கொள்கிறோம்.

முடிவுகளை அல்லது கருத்துகளை வெளியிடும் போதோ அல்லது ஆராய்ச்சியின் போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிட மாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

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

இந்த சிறப்புப் பரிசோதனைகளின் முடிவுகளை ஆராய்ச்சியின்போது அல்லது ஆராய்ச்சியின் முடிவின்போது தங்களுக்கு அறிவிக்கப்படும் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம் **பங்கேற்பாளர் கையொப்பம்**

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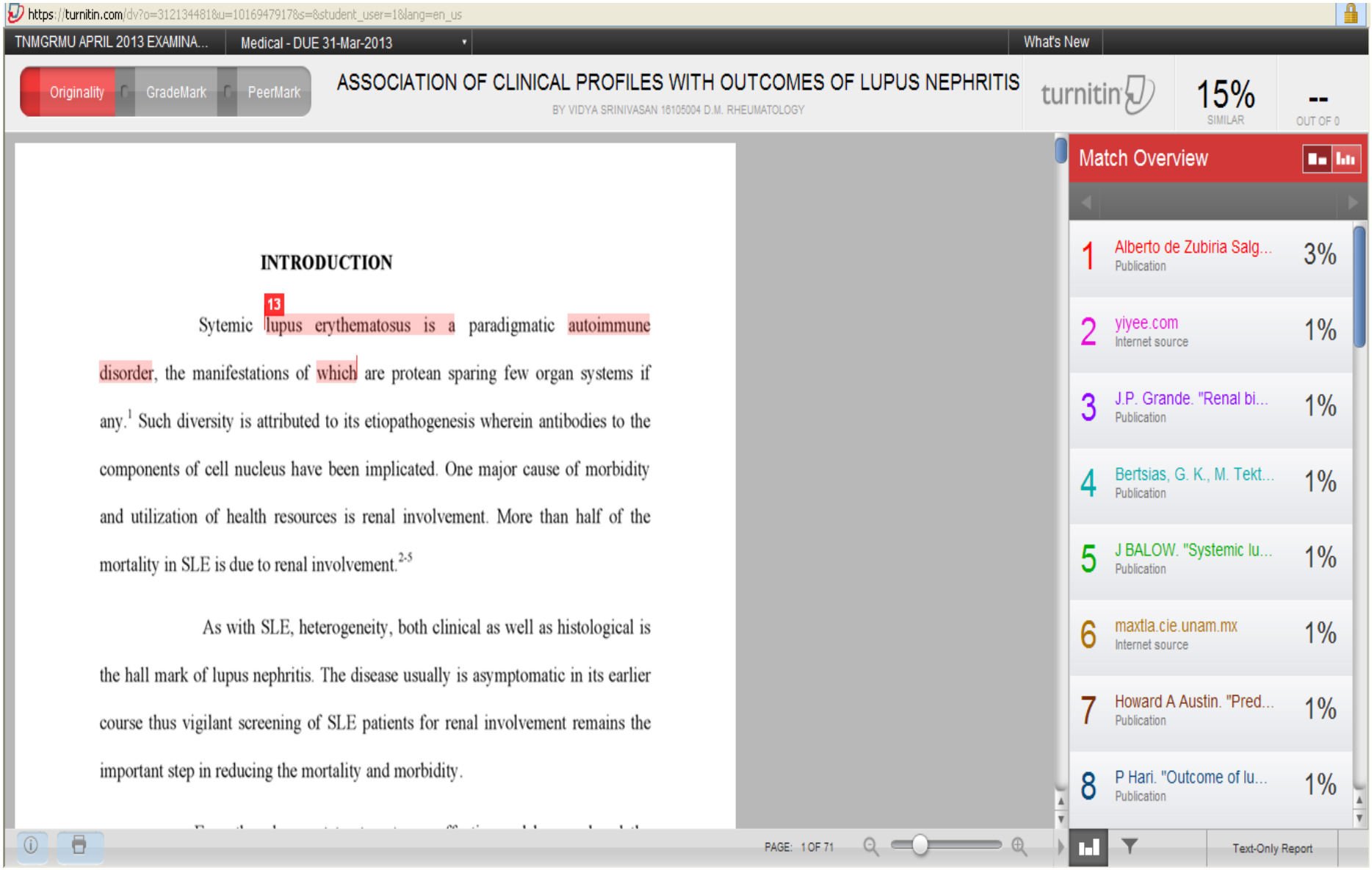
INTRODUCTION Sytemic lupus erythematosus is a paradigmatic autoimmune disorder, the manifestations of which are protean sparing few organ systems if any.1 Such diversity is attributed to its etiopathogenesis wherein antibodies to the components of cell nucleus have been implicated. One major cause of morbidity and utilization of health resources is renal involvement. More than half of the mortality in SLE is due to renal involvement.2-5 As with SLE, heterogeneity, both clinical as well as histological is the hall mark of lupus nephritis. The disease usually is asymptomatic in its earlier course thus vigilant screening of SLE patients for renal involvement remains the important step in...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INTRODUCTION
Sytemic lupus erythematosus is a paradigmatic autoimmune disorder, the manifestations of which are protean sparing few organ systems if any.[1] Such diversity is attributed to its etiopathogenesis wherein antibodies to the components of cell nucleus have been implicated. One major cause of morbidity and utilization of health resources is renal involvement. More than half of the mortality in SLE is due to renal involvement.[2-5]
As with SLE, heterogeneity, both clinical as well as histological is the hall mark of lupus nephritis. The disease usually is asymptomatic in its earlier course thus vigilant screening of SLE patients for renal involvement remains the important step in reducing the mortality and morbidity.
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