"CLINICAL PROFILE, CLINICOPATHOLOGICAL CORRELATION & OUTCOME OF ADULT MEMBRANOUS NEPHROPATHY"

Dissertation submitted in partial fulfillment of
the requirements for the degree of

D.M. (NEPHROLOGY)

BRANCH- III

DEPARTMENT OF NEPHROLOGY

MADRAS MEDICAL COLLEGE

CHENNAI-600 003

THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY

CHENNAI

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DECLARATION

I, Dr. **Abeesh.P**, solemnly declare that the dissertation titled "**CLINICAL PROFILE, CLINICOPATHOLOGICAL CORRELATION & OUTCOME OF ADULT MEMBRANOUS NEPHROPATHY"** is the bonafide work done by me at Department of Nephrology, Madras Medical College under the expert guidance and supervision of Dr. N.GOPALAKRISHNAN M.D., D.M., FRCP, Professor of Nephrology, Madras Medical College. The dissertation is submitted to the Tamilnadu Dr.M.G.R Medical University towards partial fulfillment of requirement for the award of D.M. Degree (Branch III) in Nephrology.

Place: Chennai **Dr. Abeesh. P**

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CERTIFICATE

This is to certify that the dissertation entitled **"CLINICAL PROFILE, CLINICOPATHOLOGICAL CORRELATION & OUTCOME OF ADULT MEMBRANOUS NEPHROPATHY"** is a bonafide work done **Dr.ABEESH.P**, Department of Nephrology, Madras Medical College, in partial fulfillment of the University rules and regulations for award of D.M., Nephrology under my guidance and supervision during the academic year 2011 **–** 14**.**

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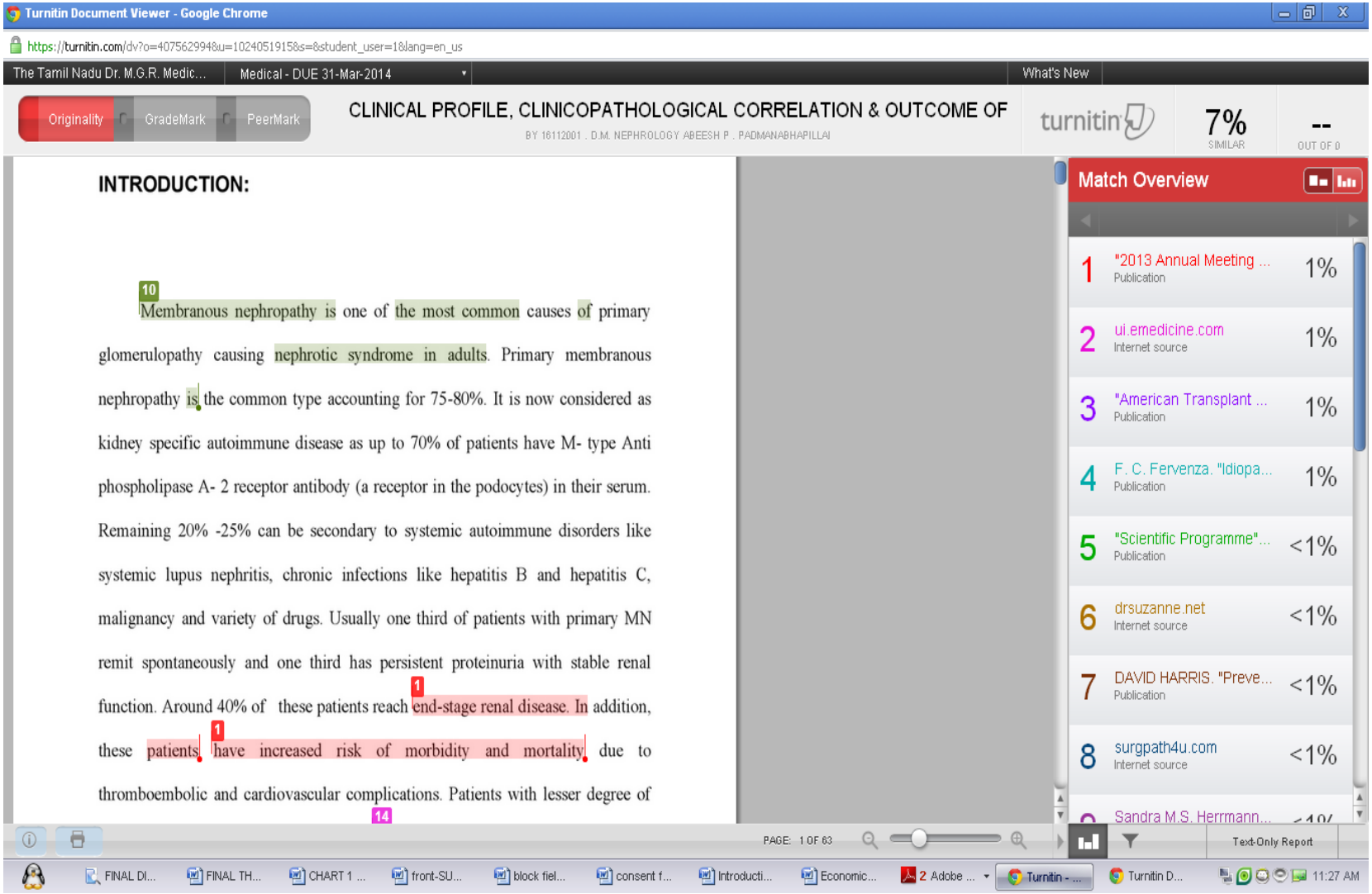
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INTRODUCTION:
Membranous nephropathy is one of the most common causes of primary glomerulopathy causing nephrotic syndrome in adults. Primary membranous nephropathy is the common type accounting for 75-80%. It is now considered as kidney specific autoimmune disease as up to 70% of patients have M- type Anti phospholipase A- 2 receptor antibody (a receptor in the podocytes) in their serum. Remaining 20% -25% can be secondary to systemic autoimmune disorders like systemic lupus nephritis, chronic infections like hepatitis B and hepatitis C, malignancy and variety of drugs. Usually one third of patients with primary MN remit spontaneously and one third has persistent proteinuria with stable renal function. Around 40% of these patients reach end-stage renal disease. In addition, these patients have increased risk of morbidity and mortality due to thromboembolic and cardiovascular complications. Patients with lesser degree of
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To
Dr.P.Abeesh,
PG in DM Nephrology,
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Dear Dr.P.Abeesh,

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled "Clinical profile, clinico patological correlation & outcome of adult membranous nephropathy" No.33082013.

The following members of Ethics Committee were present in the meeting held on 13.08.2013 conducted at Madras Medical College, Chennai -3.

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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 Nandini 26/8/13
Member Secretary, Ethics Committee

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CONTENTS

CLINICAL PROFILE, CLINICOPATHOLOGICAL CORRELATION & OUTCOME OF ADULT MEMBRANOUS NEPHROPATHY

ABSTRACT:

Background: Membranous nephropathy (MN) is one of the most common causes of primary glomerulopathy causing nephrotic syndrome in adults. Primary membranous nephropathy is the common type accounting for 75-80%. Remaining 20% -25% can be secondary to systemic autoimmune disorders like systemic lupus erythematosis, chronic infections like hepatitis B and hepatitis C, malignancy and variety of drugs. This study is aimed at analyzing the profile of membranous nephropathy in South Indian population as there is limited information in this regard.

Methods: In this prospective observational study, we included 98 biopsy proven MN patients. Five patients were excluded from the study, as they had end stage renal disease at the time of presentation. Remaining 93 patients were categorized as primary and secondary after screening for the possible causes of MN. The epidemiological profile of study population was analyzed. The clinical, biochemical and histopathological parameters among primary and secondary MN patients were compared. The response rate & predictors of response to immunosuppressive treatment evaluated. The risk factors for progression to chronic kidney disease were also analyzed.

Results: After screening for secondary causes 56/93 (60%) were diagnosed as primary MN and remaining 37/93 (40%) were secondary MN. The underlying causes of secondary MN patients were lupus nephritis (n=28), malignancy (n=3), hepatitis B virus (n=2) rheumatoid arthritis (n=1), and native drugs (n=3). Most of our primary MN patients were within 40-60 years of age 55% (31/56) and 66% (37/56) of primary MN were males. Primary MN patients had severe disease at the time of presentation when compared to the secondary MN patients (uPCR 4.75mg/mg vs.3.60 mg/mg, p=<0.001; serum albumin 3.07g/dl vs.3.49 g/dl p=<0.001; serum cholesterol 224 mg/dl vs. 184mg/dl p=<0.001).Fifty seven percent (21/37) of secondary MN had at least 1+ C1q staining when compared to 7% (4/56) in those with primary disease.

Out of 56 primary MN patients, 30 % (17/56) of patients achieved remission. Out of 33 patients who received modified Ponticelli regimen 24 % (8/33) achieved remission. Spontaneous remission occurred in 9 out of these 14 patients (64%) who were under conservative therapy. Patients who had not remitted had severe disease when compared to those who remitted. (uPCR 5.3 mg/mg vs. 3.3 mg/mg p=<0.001; serum albumin 2.8 g/dl vs. 3.47 g/dl p=<0.001; serum cholesterol 241mg/dl vs.184mg/dl p=0.0017).

During the follow up of 56 primary MN patients, (median follow up period was 18 months), 10 % (6/56) of them developed progressive renal failure. Out of the 6 patients who progressed to renal failure, 67% (4/6) had interstitial fibrosis and tubular atrophy of >25% when compared to 6% (3/50) in those who had stable renal function. Five out of 6 (83%) patients progressing to renal failure had nephrotic proteinuria as compared to 37 out of 50 patients (74%) having stable renal function. Only one patient out of 6 patients who progressed to renal failure had remitted (16%) as compared to 16 out of 50 (32%) in stable renal function group.

Conclusion:

- Primary MN was more common than secondary MN in our study accounting for about 60%.
- Primary MN was common within 40-60 years of age and males were commonly affected than females.
- Primary MN had severe disease at the time of presentation.
- C1q staining in the biopsy was more common in secondary MN
- Patients having severe disease at the time of presentation had poor remission rate (both in conservative and immunosuppressive therapy) when compared to those with mild disease.

- Interstitial fibrosis and tubular atrophy of >25% in the initial biopsy picture was a definite risk factor for progression to renal impairment. Patients with nephrotic proteinuria and those who did not remit had higher rate for progression to chronic kidney disease (not statistically significant) in our study.

INTRODUCTION:

Membranous nephropathy (MN) is one of the most common causes of primary glomerulopathy causing nephrotic syndrome in adults [1]. Primary membranous nephropathy is the common type accounting for 75-80%. It is now considered as kidney specific autoimmune disease as up to 70% of patients have M- type Anti phospholipase A- 2 receptor (a receptor in the podocytes) antibody in their serum[2,3]. Remaining 20% -25% can be secondary to systemic autoimmune disorders like systemic lupus erythematosis, chronic infections like hepatitis B and hepatitis C, malignancy and variety of drugs[2]. Usually one third of patients with primary MN remit spontaneously and one third has persistent proteinuria with stable renal function. Around 40% of these patients reach end stage renal disease [46]. In addition, these patients have increased risk of morbidity and mortality due to thromboembolic and cardiovascular complications [7]. Patients with lesser degree of proteinuria are treated conservatively by angiotensin converting enzyme inhibitors or angiotensin II receptor blocker or in combination. Though these drugs reduce proteinuria, they have no effect on disease course. Moderate to high risk patients are treated with disease specific therapy like corticosteroids, alkylating agents, Cyclosporine A, and Tacrolimus [9,46]**.** Other drugs like adrenocorticotropic hormone and selective B cells depleting agents like Rituximab have shown promising effect in some studies. But most of the time, it is difficult to

decide up on therapeutic strategy. Membranous nephropathy recurs in kidney allograft in up to 40% of those undergo renal transplant.

This study is aimed at analyzing the profile of membranous nephropathy in South Indian population as there is limited information in this regard.

Aim:

1. To study the epidemiological profile of adult MN patients.

2. To compare the clinical, biochemical and histopathological parameters among primary and secondary MN patients.

3. To evaluate the response rate & predictors of response to immunosuppressive treatment.

4. To analyze risk factors for progression to chronic kidney disease.

EPIDEMIOLOGY

Membranous nephropathy is one of the most common causes of primary glomerulonephropathy causing nephrotic syndrome in non diabetic adult population [1]. Incidence is about 1 in 1, 00,000 in general population. It accounts for 30-35% of biopsy in adult nephrotic syndrome .This increases age mounting to maximum of 50%. The peak incidence is in fourth to fifth decade of life. Onset of membranous nephropathy outside this usual range is more likely to be secondary MN. This is relatively uncommon in pediatric population (less than 5%). Adult to child ratio is 26:1.Male is commonly affected and the ratio is 2:1.Incidence and prevalence of MN in general population shows a considerable variation among geographical regions. The incidence is slightly lower in UK and is slightly higher in Greece and Macedonia .This variation is of unknown cause. This may be due to the variation in prevalence of hepatitis and malaria causing secondary MN forms.

Genetics:

Patients with HLA- DR3 have three fold increased risk for MN. HLA B8 and HLA B18 are also associated with MN among Caucasian population. In

Japanese population, MN is associated with the HLA DR 2 haplotype. Rare forms of familial MN have also been reported.

Causes of membranous nephropathy:

MN is either primary (of unknown cause) or secondary to varying etiologies like infections, drugs, toxins, autoimmune diseases and malignancy. Diagnostic work up differs significantly between the two forms. Also for secondary MN, therapy is focused on underlying cause but idiopathic MN is treated with immunosuppressant drugs. Most common type is primary MN, accounting for about 75%.

Primary MN:

Primary MN remained as a diagnosis of exclusion till 2009, when Beck et al demonstrated autoantibodies against M–type PLA2R, a membrane glycoprotein located in the podocytes in 60%-80% of such patients. This landmark discovery supports the notion that idiopathic MN is an organ limited autoimmune disease [37,38,39,40].

Secondary MN:

Secondary MN may be due to systemic autoimmune disorders like systemic lupus nephritis, rheumatoid arthritis, chronic viral infections like hepatitis B and hepatitis C, malignancy, variety of drugs and alloimmunity like hematopoietic stem cell transplant. Secondary MN can be suspected to some extent by few characteristic pathological features in renal biopsy along with evidence of systemic features or drug intake. Correction of the systemic illness or withdrawal of the offending drug resulting in remission of the disease shows that the MN is of secondary type [23].

It should be noted that cause of the MN may be primary though secondary causes can co-exist with it, as shown in few studies.IgG4 in renal biopsy, which is characteristic of primary MN was demonstrated in some MN associated with malignancy and hepatitis B infection.

Autoimmune disorders:

Most common type of autoimmune disorder causing secondary MN is systemic lupus erythematosis. Lupus nephritis class V as per ISN/RPS classification accounts for 10-20% of renal involvement in systemic lupus erythematosis. It usually affects young females. It is indistinguishable from

primary MN clinically. High degree of suspicion is required as nephrotic syndrome predates onset of other systemic manifestations of lupus erythematosis. Also these patients have normal complement levels with undetectable or low ANA levels. Biopsy shows mesangial and or endocapillary proliferation with thickening of capillary basement membrane. Immunofluorescence shows varying immune and complement deposits to the tune of full house pattern with immunoglobulin of non IgG4 type. Course of the disease is similar to that of primary MN and has relatively good long term prognosis compared to class III or class IV lupus nephritis.

Rheumatoid arthritis as such or therapeutic drugs like gold, penicillamine, bucillamine (which were used previously for rheumatoid arthritis) or nonsteroidal anti inflammatory drugs can cause MN. Ankylosing spondylitis, autoimmune thyroiditis, IgG4 related disease and Sarcoidosis, Systemic sclerosis, Dermatomyositis, Graves's disease, mixed connective-tissue disease and Sjögren syndrome are other autoimmune disorders associated with MN. Whether they are true causative etiologies or just coincidental is not known.

Infections:

Persistent antigenemia due to long standing infections causes MN. These include viral infections like chronic hepatitis B infection and hepatitis C infection

(common is membranoproliferative pattern of glomerulonephritis and cryoglobulinemic glomerulonephritis) [17,28], human immunodeficiency virus, chronic malarial infection, enterococcal endocarditis, syphilis, leprosy, hydatid cyst, schistosomiasis and filariasis. This is supported by the fact that on treating these infections, proteinuria remits and pathogenic antigens formed from the parasites have been isolated from the immune complex deposits in the glomeruli.

Among Asian race 30-40% of infection associated MN is due to chronic hepatitis B viral infection. These patients show surface antigen, anti-core antibody and e-antigen positive in their serum with normal or mild elevation of transaminases. The e antigen was separated from the immune complex deposits confirming its pathogenic potential in causing the disease. MN related to hepatitis B infection and lupus nephritis class V are only two MN associated with hypocomplementemia. Treatment of infection with antiviral drug results in remission of disease.

Malignancy:

Elderly MN patients have increased incidence of malignancy when compared to general population .It is said that MN can precede, occur with or succeed onset of other symptoms related to malignancy. Common malignancies associated with MN are solid organ tumors like lung carcinoma, gastrointestinal

malignancy (colon& stomach), prostatic carcinoma in males and carcinoma breast in females. Other rare associated malignancies include non Hodgkin's lymphoma and chronic lymphocytic leukemia. Carcinoembyonic antigen has been demonstrated in the immune deposits in glomeruli. So it is advisable to screen every elderly MN patients for occult malignancy.

Drugs and toxins:

Drugs like gold, penicillamine or bucillamine which were used previously for Rheumatoid arthritis or nonsteroidal anti inflammatory drugs, captopril, lithium probenecid and mercurial compound can cause MN. Temporal profile exists between the drug exposure and onset of symptoms. Remission of proteinuria occurs in months to years after withdrawing the offending drug.

Alloimmunity:

Membranous nephropathy develops when immune system is exposed to non self antigen chronically such as in renal transplantation and hematopoietic transplantation. This is supported by the fact that denovo MN developing post renal transplant .MN occurring after hematopoietic stem cell transplant may be due to graft versus host reaction. Rare form of MN in neonates of mother having neutral endopeptidase deficiency is also due to alloimmunisation.

Evolution of concept of Pathogenesis:

In 1959, the first insight of pathogenesis of primary MN was provided by Walter Heymann through his rat models .There are two models of Heymann nephritis viz one the active model and other the passive model. Active model was developed by immunizing rats with either emulsion of whole rat cortex in complete Freud's adjuvant or with purified complex of 600 kd glycoprotein. This resulted in development of antibodies against these antigens within 2 weeks. The immune complex was demonstrated in the glomerulus in 3-4 weeks, proteinuria occurred in 6-8 weeks and nephrotic syndrome developed in 12 weeks which continued to persist till they die. Passive Heymann model was induced by injecting heterologus anti serum to rat Fx1A or antiserum for megalin. This resulted in much rapid onset of the disease when compared to active model. Here the glomerular deposits occurred within minutes and proteinuria developed in 7 day. This phase was known as the heterologus phase as the antibodies deposited in the glomerulus were not self. This phase is followed by the autologus phase in which autoantibodies are formed against these heterologus antibodies deposited in the glomerulus. This resulted in further worsening of proteinuria. However, this model could not be induced by immunizing antigens derived from organs other than kidneys. Heymann concluded that primary MN had autoimmune basis and named membranous nephropathy as "**autoimmune nephrosis**".

The histopathological picture of Heymann's model resembled human MN. This made him to believe that human MN could be an autoimmune disease of kidney. This was also supported by the coexisistance of MN disease with other organ specific autoimmune disease like type 1 diabetes mellitus, myasthenia gravis, Graves' autoimmune throiditis, and primary biliary cirrhosis and so on.

Germuth and Dixon proposed that the glomerular deposits were due to deposition of circulating immune complex. They believed that these immune complexes dissociate, traverse across the glomerular basement membrane, reunite and get deposited in the sub epithelial space. On the contrary Van Dame et al and Couser et al demonstrated that ex vivo perfusion of bloodless kidney (which were devoid of circulating antigen and immune complex) with heterologus antiFx1A antiserum resulted in sub epithelial deposits as that of MN. This suggested that antibodies are formed against in situ antigens and not planted antigens or circulating immune complexes. This antigen in Heymann's model was identified as *megalin.* Surprisingly this is not present in glomerulus of human kidney. Since then, various studies were conducted to identify the target antigen in the glomerulus.

Bovine Serum Albumin - related membranous nephropathy:

A study showed that few childhood membranous nephropathy patients had high levels of circulating cationic bovine serum albumin and anti–bovine serum

albumin antibodies. Bovine serum albumin was demonstrated in the immune deposits in glomerulus. This bovine albumin is present in cow's milk and beef protein .This escapes the intestinal barrier and cause antibody formation. It is of cationic charge and binds to the anionic glomerular capillary wall which results in immune complex formation. Eliminating this environmental factor from the diet may be beneficial in these patients [4].

Neutral endopeptidase - related membranous nephropathy in neonates:

Ronco and Debiec by their elegant study demonstrated the target antigen in neonatal MN, a rare disease entity in human being. Mothers lacking a podocyte membrane protein namely neutral endopeptidase, who were alloimmunized by previous pregnancy, delivered new born with MN in subsequent pregnancy. This was due to transplacental transfer of antibodies from these sensitized mothers to their fetuses resulted in insitu immune complex deposition in them akin to MN. This disease is of transient phenomenon as the disease resolves within few months after birth with the clearance of these maternal IgG antibodies from the circulation [5].

Role of APLA2R1 in the pathogenesis of primary MN:

By Western blot technique, Beck et al in 2009 demonstrated that PLA_2R1 is the major target antigen for idiopathic membranous nephropathy. Phospholipase A_2 Receptor is a 185 KD type 1 transmembrane receptor of mannose receptor family with large extra cellular N terminal domain, small transmembrane domain and intracellular C terminal domain .It is expressed on the normal podocytes .This receptor exists in two forms; one the extended form and other the bent form. Antibody to this receptor has been demonstrated in patients with primary MN .This antibody is exclusively of subclass IgG4, which is incapable of activating complement cascade .This explains the lack of active inflammation and indolent course of primary MN. Antibodies can recognize only the conformation dependent target epitope antigen present in the receptors and binding of the antibody occurs in one of these two configurations. Normal physiological function of this receptor is unknown. It has been suggested that it has a role in positive regulation of mitogen activated protein kinase activation and reactive oxygen species production & negative regulation by internalization and degradation of PLA_2. The triggering event that causes this antibody formation and the mechanism of proteinuria occurring after antibody binding with this receptor are yet to be identified. Formation of in situ immune complex with IgG4 resulted in slow activation of complement cascade forming complement membrane attack complex (C5b-9) in

sublytic quantities. This gives oxidative stress to the podocytes causing stimulation of oxygen radical producing enzymes in the podocytes. Subsequently, cytokines including transforming growth factor- beta (TGF-beta) formed as the result of this oxidative stress along with complement membrane attack complex (C5b-9) cause cytoskeletal alteration in podocytes and abnormalities in slit diaphragm. This results in podocyturia and proteinuria [21,22,27,30].

B cells also have a role in pathogenesis of MN possibly acts as antigen presenting cells. Immunohistochemistry also demonstrated B cell infiltration in the kidney of MN patients [27].

By western blot technique, circulating antibodies against this antigen were demonstrated in about 70% of patients with primary membranous nephropathy. However this technique is not suitable for most diagnostic laboratories for analyzing large sample size. To overcome this limitation, in 2011, Hoxha et al identified these antibodies by indirect immunofluorescence assay which can be used for routine laboratory purposes. He also demonstrated that antibody titers correlated with disease severity and response to treatment .He showed that immune remission occurred prior to clinical remission. This test is helpful in monitoring the disease status and response to treatment. Other method recently developed for antibody detection is ELISA. Studies showed that Western blot, ELISA technique and indirect immunofluorescence assay had concordant results.

Ronco et al demonstrated enhanced expression of PLA2 receptors in podocytes by immunohistochemistry in idiopathic membranous nephropathy patients. Out of 31 patients having PLA_2R1 positivity, 10 patients had no circulating antibody. Rapid clearance of antibody from blood which got deposited in glomeruli or late referral of patients with persistent proteinuria due to irreversible ultrastuctural changes might be the probable causes. He concludes that absence of anti –PLA_2R1 antibody does not rule out PLA_2R1 associated membranous nephropathy.

Cumulative data from various studies so far has shown that this assay is 100% specific for primary membranous nephropathy as it is not detected in patients with secondary membranous nephropathy or in patients with nephrotic syndrome of other pathology or in normal individuals .It has sensitivity of 70% to 80% .This might be due to fluctuating antibody levels with disease activity or antigens other than PLA_2R1 like superoxide dismutase 2 (SOD 2), aldose reductase(AR) and α enolase might be the target in these patients[51,52,53,54]. It has been shown by few initial studies that this antibody was positive in some of the secondary MN patients like MN due systemic lupus erythematosis or malignancy. However later studies showed that these patients found to have only IgG4 subtype antibodies in their renal biopsy tissues which is characteristic of primary MN.

Hence it was concluded that these patients had primary MN co existing with these systemic diseases.

Primary membranous nephropathy has 30% to 40% recurrence rate post transplant and more so with identification of Anti –PLA_2R1 antibody prior to transplant. Studies identified these antibodies in 50% to 80% of patients with recurrent primary membranous nephropathy and not in de novo membranous nephropathy [6]. Advantages of Anti –PLA_2R1 antibody estimation is given in Table 1.

Table 1: Advantages of estimating Anti –PLA_2R1 antibody

- Simple non invasive, cost effective method.
- Avoids extensive diagnostic procedures for ruling out secondary causes.
- Correlates with disease activity including relapse and severity of disease.
- Useful for monitoring treatment.
- Avoids unnecessary exposure to immunosuppressive drugs.
- Predicts post renal transplant recurrence.
- Differentiates recurrence from de novo membranous nephropathy.

Even though demonstration of this antibody in patients with nephrotic syndrome is diagnostic of primary MN, it would be too early to abandon kidney biopsy in such patients. *Hofstra et al* suggested renal biopsy as the method of diagnosing MN. In future, it may be useful as diagnostic biomarker and for monitoring response to therapy. Need for the day is developing animal models by passive transfer of the a-PLA2R antibody and demonstrating MN in them and proving Koch's postulate for the cause and the effect.

Pathogenesis of secondary MN is usually due to the circulating immune complex or planted antigens.

PATHOLOGY:

Membranous nephropathy derives its name from histopathological feature of thickened glomerular basement membrane. In addition, it shows pinholes and spikes on JONES silver methanamine staining. All glomeruli show pathological changes such that single glomerulus showing spikes is sufficient for diagnosing MN [18].

Classical MN shows the following features in histopathology:

- Light microscopy:

  This shows normal mesangium and normal cellularity in the glomerulus; the capillary walls are diffusely thickened and capillary lumina are patent; with trichome stain it shows subepithelial fuchsinophilic deposits; and in silver methanamine staining they show the characteristic spikes pattern.

- Immunofluorescence microscopy:

Immunofluorescence shows diffuse granular immunoglobulin deposits usually IgG and C3, along the capillary walls. Few IgM deposits can be seen suggesting non specific entrapment.

- Electron microscopy :

Electron microscopy shows sub epithelial deposits. Based on the location of the deposits MN has four stages.

Stage 1:

Normal by light microscopy, but on electron microscopy, few electron-dense deposits is seen in the subepithelial space along the capillary walls.

Stage 2:

Numerous and larger deposits in the subepithelial space with spikes from basement membrane are seen on either sides of the deposits.

Stage 3:

New extracellular material surrounds the deposits having chain like appearance; electron dense deposit is now surrounded by the basement membrane so that subepithelial deposits now become intramembranous in position.

Stage 4:

Resolution phase in which initial electron dense deposits become electron lucent, and capillary walls become irregular and thickened.

Histopathological features that favor secondary MN:

There are few pathological findings in the renal biopsy that may give us some clues to suspect secondary MN

Lupus nephritis class V:

- presence of mesangial or endocapillary proliferation
- full house pattern of immunoglobulin deposits including staining for C1q in immunofluorescence staining.
- glomerular deposits predominantly containing immunoglobulin other than IgG4
- electron-dense deposits in the sub endothelial location of the capillary wall
- mesangium or along the tubular basement membrane and vessel walls under electron microscope
- endothelial tubuloreticular inclusions under electron microscope

Drug-associated secondary MN

- Electron microscope MN shows only a few superficial scattered subepithelial deposits

Histopathological features as predictors for remission in primary MN:

Few studies tried to assess the histopathological features in renal biopsy as predictors for remission in primary MN patients. They showed that neither the severity of tubulointerstitial and vascular lesions nor by the degree of complement deposition in the glomerulus could predict the remission in these patients.

In one study, it was observed that in electron microscopy, subepithelial homogeneous deposits showed better response to treatment than those with subepithelial and intramembranous heterogeneous deposits and this had better long term prognosis. But the staging under electron microscope could not predict the remission.

Histopathological features as predictors of progression to CKD:

Studies showed that presence of chronic irreversible chances in histopathology viz. the presence of tubulointerstitial fibrosis , focal glomeruli sclerosis, and chronic vascular sclerosis have been associated with increased risk for progression to renal failure . A study conducted in Japan showed that on multivariate analysis, tubulointerstitial lesions ≥20 percent of the renal biopsy area was one of the significant predictors of progression to end-stage renal disease.

However, they cannot independently predict the rate of disease progression. Moreover, baseline clinical variables along with these findings are needed to decide upon therapeutic strategy. Similarly, neither the stage nor the amount of complement C3 deposition predicts renal survival.

Interestingly, these chronic changes in histopathological findings are associated with old age, hypertension and lower creatinine clearance at the time of presentation.

Clinical Manifestation:

MN is insidious in nature, takes long time to manifest clinically. It has neither prodromal symptoms nor any antecedent trigger like infections. Most common presentation is nephrotic syndrome accounting for 60-70%. Proteinuria is non selective in MN unlike minimal change disease which has selective proteinuria. Approximately 80% of these patients have edema with or without features of anasarca. Patients rarely have pericardial and pleural effusions only if proteinuria is severe. Patients may also present with nonspecific complaints of anorexia, malaise, and fatigue. Thirty to forty percent of patients have subnephrotic proteinuria. They are diagnosed in routine evaluation for some other illness. In an

unpublished observation, Daniel C. Cattran noted that around 60% of this asymptomatic group will progress to nephrotic syndrome over a span of 1-2 years.

Microhematuria can occur in 50% of patients with primary MN, but macrohematuria is rare. Presence of microhematuria, macrohematuria or RBC cast in MN is more likely towards secondary form. Most of these patients have normal blood pressure at the time of presentation. Hypertension occurs only in 10-20% of patients at the time of presentation.

Renal failure at the time of presentation is uncommon accounting for around 10-15%. Nephrotic syndrome patients are more prone for thromboembolic manifestations and more so in case of MN patients for unknown reasons even after adjusting for quantum of proteinuria[7] .MN is the most common cause of renal vein thrombosis which can occur in 5 -50%.Other sites of thromboembolism are deep vein thrombosis, pulmonary embolism. Occurrence of thrombotic episode correlated with disease severity. These are more common in patients with heavy proteinuria and severe hypoalbuminemia (<2 g/dl).

These patients have high risk for atherosclerotic coronary artery disease due to hyperlipidemia. Other clinical manifestations are hypothyroidism, anemia and vitamin D deficiency due to loss of corresponding transfer or binding protein in the urine.

Good prognostic indicators are female sex, children and young adults, subnephrotic range proteinuria, a progressive decline in proteinuria, and presenting with normal creatinine clearance. In addition, patients belonging to Asian race found to have a better long-term prognosis than other ancestries. Attainment of remission, either spontaneously or by drugs has good long-term outcome. As shown by one study, greater than 50 percent reduction in protein excretion at one year has high probability of spontaneous remission.

Acute decline in renal function in known primary MN patient:

Progressive renal failure in MN typically occurs in more gradual pattern. Some patients can have an acute decline in renal function. In such situation, the following conditions should be excluded.

- Acute bilateral renal vein thrombosis which can occur in 5 -50%.This may be associated with flank pain, macrohematuria and reduction in renal function.
- Drugs inducing acute interstitial nephritis, such as diuretics, non steroidal anti inflammatory drugs and antimalarial drugs in which white cell, white cell casts, and possibly eosinophils are typically seen in the urine sediment.

- Superimposed crescentic glomerulonephritis, in which red cells and cellular casts are found in the urine sediment. Rarely MN can be associated with antineutrophilic cytoplasmic antibody associated vasculitis and anti glomerular basement membrane disease.
- Intravascular volume depletion and massive nephrosarca.

Secondary MN:

Clinical presentation of secondary MN depends on the underlying cause of MN. In patients with drug induced MN, proteinuria remits on stopping the offending drug (e.g. gold, penicillamine or nonsteroidal anti inflammatory drug).Remission will occur in 9-12 months period , but it may take even 2-3 years for achieving remission. For MN secondarily to autoimmune disease like systemic lupus erythematosis, treating the underlying cause will result in remission. Treating underlying malignancy or viral infection can cause reduction in proteinuria.

Natural history and Prognostic factors:

Primary MN can be divided into three groups based on nature history in untreated patients (rule of three) [25,46].

- Spontaneous remission of proteinuria occurs in 5-30% at 5 years
- Persistent proteinuria with stable renal function occurs in 25- 40 % at 5 years
- Progressing to end stage renal failure occurs in 14% at 5 years, 35% in 10 years and 41 % in 15 years.

As significant numbers of patients have spontaneous remission, in the view of unacceptable toxicity of the drugs used to primary MN, it is advised to continue conservative line of management for reasonable duration so as to achieve spontaneous remission**.**

Predictors for progressing to end-stage renal disease:

Prognosticating any disease is very essential for deciding the management strategy. An accurate predictor of renal outcome of patients in primary MN may be helpful for separating patients who are likely for progressing to renal failure. This would prevent low risk group from exposure to the toxic immunosuppressant drugs. But till now no such accurate predictor exist for primary MN patient. The

following are clinical and biochemical parameters that may be used as predictors for progression to end stage renal failure [32,47,48,49].

- older age at onset (particularly greater than 50 years)
- male sex
- nephrotic range proteinuria (particularly if protein excretion exceeds 8 to 10 g/day)
- lower initial creatinine clearance [sr. creatinine ≥1.5 mg/dL (≥133 micromol/L)]
- the rapid rate decline in creatinine clearance

Toronto Glomerulonephritis Registry defines risk for progression to renal insufficiency in patients with primary MN. Based on quantum of proteinuria and creatinine clearance at the time of presentation, they classify patients as low, moderate and high risk (Tab.2).Low risk patients has less than 10% chance for progressing to end stage renal disease in 10 years as compared to high risk patients having as high as 80% probability for progressing to end stage renal disease at the end of 10 years.

Table .2: Toronto Glomerulonephritis Registry risk stratification.

RISK	uPCR (mg/mg)	GFR (ml/min/1.73 m2)	% of progression to ESRD(10 yrs)
Low	<4	>60	<10%
Moderate	4-8	>60	55%
High	>8	>60 or < 60	66-80%

This stratification is meant for progression to chronic renal disease only. This will not hold good for other complications of nephrotic syndrome like atherosclerosis due to hypercholesterolemia and thromboembolic complications due to the hypercoagulable state.

As per van den Berg in his study urinary biomarkers such as α1 microglobulin, β 2- microglobulin, are comparable to quantum of proteinuria in predicting the patients who are at risk for progression to end stage renal failure. But non availability of these markers limits their clinical utilization [21,33].

MANAGEMENT

Investigations:

It is of paramount importance to differentiate primary from secondary MN as the therapeutic protocol differ entirely for them. Secondary MN remits by treating the underlying cause but primary MN may need toxic immunosuppressant drugs. Following investigations are done as and when MN is diagnosed in the renal biopsy.

Urine analysis:

Urine microscopy:

- For any red blood cells and red blood cells cast.
- Quantification of urinary protein excretion.
    - uPCR or 24 hours urine protein estimation.

Blood urea nitrogen, serum creatinine and creatinine clearance.

Liver function test.

Antinuclear antibodies, anti–double-strand DNA, complement levels.

Hepatitis B, hepatitis C serology.

Syphilis serology.

Lipid profile.

Malignancy workup:

Age and gender appropriate health screening such as, mammography, motion for occult blood, upper gastrointestinal endoscopy, sigmoidoscopy, X ray chest, prostate specific antigen.

Other investigations according to clues from the initial patient history and physical examination.

Newer investigations.

Antiphospholipase A2 receptor antibody assay

For diagnosis and monitoring therapy

Urinary biomarkers for risk stratification

- IgG excretion rate.
- Urinary beta-2 micro globulin [33].
- Urinary C5b-9 [21].

Treatment of primary MN:

Goal of treating primary MN is to preserve the renal function by reducing the proteinuria and minimizing complications from nephrotic syndrome. It is a known fact that about one third of MN undergoes spontaneous remission. Hence not all patients require immunosuppressant drugs .Also these drugs have serious adverse effect. Risk and benefit of treating with immunosuppressant drugs should

be weighed before starting on these drugs. Most of the time, it is difficult to make decisions regarding treatment protocol [16].

Conservative treatment:

As discussed previously, there is high rate for spontaneous remission in primary MN patients. Only those patients with high risk for progression to renal failure or those having complications of nephrotic syndrome should receive potent immunosuppressive treatment. But all most all patients are candidates for conservative therapy. Conservative therapy includes angiotensin inhibition, lipid-lowering and anti coagulants in selected patients .Other supportive therapy includes control of edema with anti diuretics and nutrition support [46].

RAAS inhibition:

Renin angiotensin adosterone inhibitors are recommended in all most all patients with MN for reducing proteinuria. It acts by lowering the intraglomerular pressure by inhibiting angiotensin mediated efferent arteriolar vasoconstriction. They are also recommended in chronic kidney disease patients having proteinuria along with monitoring serum potassium level. The optimal proteinuria goal in patients with chronic kidney disease is less than 1000 mg/day.

But this is difficult to achieve in MN patients. Though it reduces proteinuria, studies show that it does not alter the course of the disease.

The evidence for a renal protective effect with ACE inhibitors or ARB is relatively weak in MN patients. Achieving partial remission is helpful, as studies has shown that partial remission by itself was independently associated with slower decrease in renal function and a lower incidence of renal failure in long run.

Target blood pressure:

As in other proteinuric kidney diseases, optimum blood pressure would be less than 130/80 mmHg. By attaining this target blood pressure, progression to chronic kidney disease is reduced. Reduction in blood pressure has two advantages i) reduction in proteinuria, ii) significant reduction in cardiovascular risk (as these patients are associated with high risk for cardiovascular disease).

A low salt diet is an important part of antihypertensive therapy (especially when using angiotensin inhibitors) and control of edema in patients with MN. Also, a high salt diet can increase proteinuria. In some individuals, a high salt diet would be the cause of worsening proteinuria rather than increased immunological activity reaction.

Other drugs including diuretics for correcting volume overload may reduce blood pressure. Diuretics cause symptoms like fatigue, orthostatic hypotension or decreased tissue perfusion as evidenced by elevation in the blood urea nitrogen and/or serum creatinine concentration as adverse effects.

Lipid lowering drugs.

Hyperlipidemia occurring due to nephrotic syndrome is a risk factor for cardiovascular disease in MN patients. Elevation in the serum cholesterol concentration is treated by statins which has pleotropic effect including endothelial protection and reducing cardiovascular disease.

Anticoagulants.

Patients with nephrotic syndrome due to MN in particular are at increased risk for thromboembolic events .This risk increases drastically in patients with serum albumin of less than 2.5 g/dl. KDIGO suggests prophylactic anticoagulation in these patients or those who developed deep vein thrombosis. Initially these patients should be treated with low molecular weight heparin or unfractionated heparin followed by oral anti coagulants.

Immunosuppressive Therapy:

Immunosuppressive drugs are indicated only for patients under high risk group as per Toronto risk group stratification. Various immunosuppressive drugs have been tried for primary membranous nephropathy patients. First-line immunosuppressive therapy consists of cytotoxic drugs like alkylating agents plus glucocorticoids .If alkylating agents are contraindicated, calcineurin inhibitor with low dose glucocorticoids is given [35]. Patients who do not respond to one regimen are usually treated with the other, and those with resistant disease may be treated with Rituximab. Adrenocorticotropic hormone has also been tried in few studies.

Alkylating agents:

Ponticelli regimen is used for treating patients under moderate to high risk category [31, 55, 56]. This regimen includes Methyl prednisolone 1 g intravenously once daily for 3 days followed by oral prednisolone 0.5 mg/kg for 27 days .This is followed by Chlorambucil orally for 30 days at a dose of 0.2 mg/kg. This constitute for one cycle. This is repeated for 3 cycles. Five and ten year's remission was 40 % and 47% and 5 and 10 years ESRD were 10% and 40% respectively. In modified Ponticelli regimen Chlorambucil is replaced by Cyclophosphamide at a dose of 2 mg/kg orally. Jha et al from India also compared this regimen with supportive treatment and followed up for 10 years. This study

also confirmed results of Ponticelli**.** There are both short and long term toxicities for cyclophosphamide. Short term toxicities include bone marrow suppression, infection, alopecia, cystitis, seizures. Long term toxicities include cancer like non melanocytic skin malignancy and bladder cancer and infertility in men and women.

Table.3: Trials including alkylating agents in primary MN [46].

Trial	Treatment	Follow up (months)	Remission	Renal survival
Ponticelli (RCT)	Chlorambucil & Prednisolone	120	83 vs. 38	92 vs. 60 (10 yr)
Jha (RCT)	Cyclophosphamide & Prednisolone	130	72 vs. 24	89 vs. 65(10yrs)
Torres	Chlorambucil & Prednisolone	48	42 vs. 0	90 vs. 20 (7 yrs)
Du Buf	Cyclophosphamide & Prednisolone	51	86 vs. 20	86 vs. 32 (5 yrs)

Calcineurin inhibitors:

Few studies showed the efficacy of both Cyclosporine and Tacrolimus in patients with primary MN in reducing proteinuria and prevention of progression to ESRD when combined with steroids. One study by Cattran et al showed that Cyclosporine at 3.5 mg/kg/day for 12 months reduces proteinuria by 50% in 50% of patients and may slow progression the progression of renal failure. The relapse rate was about 50% after discontinuing the drug.

Regarding Tacrolimus, study done by Chen et al showed that Tacrolimus with steroids has equal efficacy to that of cyclophosphamide with steroids. But there is increased incident of adverse effect like diabetes mellitus, hypertension and infection in patients treated with Tacrolimus.

Mycophenolate mofetil:

Pilot studies done by Chan , Nayagam and Branten et al showed that MMF is not inferior to cyclophosphamide in treating primary MN patients. Long term effect of this drug is not known. Randomized control trials are needed using MMF to decide up on its role in these patients. KDIGO does not recommend MMF as monotherapy in primary MN patients [10,11,20].

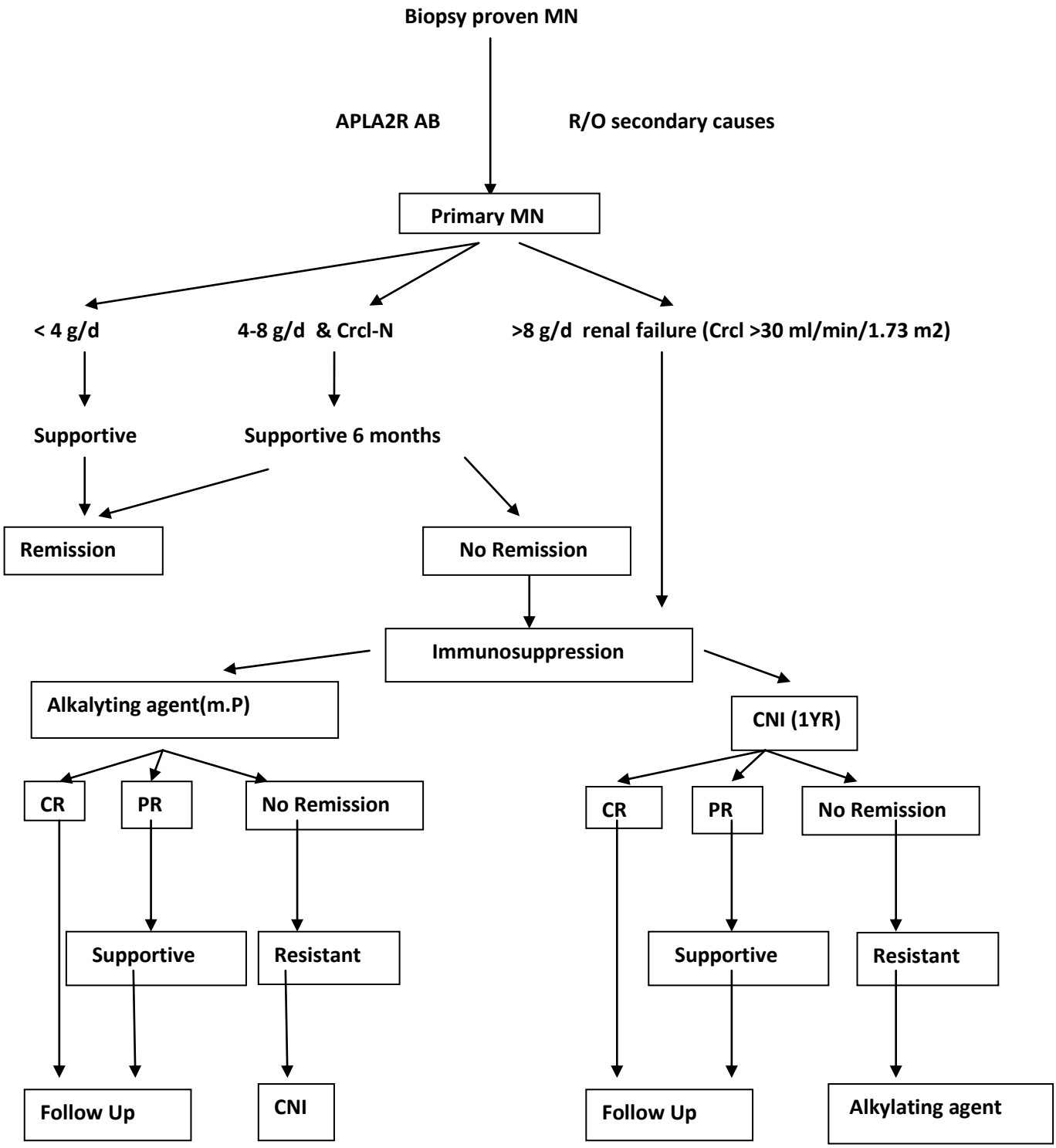
Rituximab:

Rituximab is anti B cell (CD 20) monoclonal antibody. Studies have shown that Rituximab effectively reduced the proteinuria in patients with primary MN more so if they are resistant to first line drugs. Ruggenenti et al showed that patients having minimal interstitial fibrosis and tubular atrophy had good response to this drug compared to those with severe interstitial fibrosis and tubular atrophy. Anti APLA2R antibody titer was reduce after Rituximab therapy.The major alarming side effect of this drug is progressive multifocal leucoencephalopathy which occurred in 80% of the patients receiving this drug [11,12,13,14,15].

Adrenocorticotropic hormone:

Berg et al in his publication in 2009, in 30 patients who received ACTH had reduction in proteinuria and improvement in serum albumin during a follow up of 3- 13 years. He concluded that ACTH therapy is equally efficacious as that of methyl prednisolone and alkylating agent. Few follow up studies also showed promising results. Till now there is no randomized control trial for ascertaining its position in the management of primary MN.

Guidelines for management of MN



CR : Complete Remission , PR :Partial Remission , CNI : Calcineurin Inhibitors,

MP: modified Ponticelli Regimen

Relapse :

Sub nephrotic proteinuria - supportive treatment

Nephrotic syndrome - Repeat initially responded regimen only once

Indication for repeat biopsy: Rapid rise in sr. creatinine (30% in 2 months)

Supportive treatment:

Antiproteinuric drugs

Antihypertensive drugs

Lipids lowering drugs

Anticoagulant prophylaxis (if sr.albumin < 2.5 g/dl)

Prophylaxis for long term steroids:

Pnemocystis jeroversi prophylaxis

Osteoporosis

Second line drugs:

Rituximab.

Adrenocorticotropic hormone (ACTH).

MATERIALS AND METHODS:

Institutional ethical committee approval was obtained for the study. This is prospective observational study conducted during the period of March 2012-February 2014 in the Department of Nephrology, Madras medical college, Chennai.

INCLUSION CRITERIA:

- Age between 12 -75 yrs
- Biopsy proven membranous nephropathy patients.

EXCLUSION CRITERIA:

- Pregnant patients
- Unwilling patients
- End stage renal disease patients (e GFR < 30 ml/min/1.73 m2)

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Patients with biopsy proven MN, who got treatment under our department within the study period, were included in the study. Detailed clinical history of edema, oliguria, abdominal distension and other relevant history were taken. History suggestive of secondary causes like joint pain ,early morning stiffness, skin rash, photosensitivity, breathlessness, for connective tissue disorders, loss of weight, and appetite, swelling anywhere in the body, hemoptysis, hematemesis, vomiting, alerted bowel habits for malignancy, past or recent history of jaundice, blood transfusion for hepatitis B, and other detailed drug history was obtained. Other history includes history regarding comorbid illness and personal history. Detailed clinical examination including blood pressure examination in all 4 limbs and complete systemic examination were done. Those with blood pressure >140/90 were diagnosed to have hypertension.

Patients were subjected to routine urinary examination including urine for protein, deposits like red blood cell, white blood cell. Urine was analyzed for red blood cell cast, white blood cell cast also. Urine protein/creatinine ratio was measured. Patients underwent routine hematological investigation like blood hemoglobulin, total count, differential count, peripheral smear study. Blood investigation viz. blood sugar, blood urea, serum creatinine, serum electrolyte, lipid profiles were taken. GFR estimated by Cockcroft Gualt equation (ml/min/1.73 m2). Liver function test including serum bilirubin and liver enzymes

were taken. .Urine for culture and sensitivity, blood for culture and sensitivity and for malarial parasites were done. All patients screened for viral serology like hepatitis B, hepatitis C infection and human immunodeficiency virus. Appropriate patients were screened for other serological markers including antinuclear antibody, anti double stranded-DNA, complement levels. Chest X ray PA view and electrocardiography, upper gastrointestinal endoscopy and motion for occult blood were done in all patients. Ultra sonogram of abdomen, ultra sonogram kidney and urinary tract done for assessing size of kidney, cortical echogenesity, and corticomedullary differentiation was done. Appropriate patients were also screened for C.T chest, prostate specific antigen for males and mammography for female patients.

Histopathological features of renal biopsy at the time of presentation including C1q staining and interstitial nephritis and tubular atrophy were noted.

ANALYSIS:

Biopsies proven MN patients were categorized into primary and secondary after screening for secondary causes. Secondary MN patients were labeled according to the underlying cause. Both the groups were analyzed under clinical biochemical and histopathological parameters.

In primary MN group, patients were treated according to KDIGO guidelines their remission rates were assessed. The clinical biochemical and histopathological parameters were analyzed both in patients who achieve remission and those who did not. All the primary MN patients were followed up regularly. Patients who progress to end stage renal disease were assessed and the predictors of were analyzed.

Clinical data:

Patients were categorized into three groups according to their risk of progression to chronic kidney disease. Low risk was defined as urine protein creatinine ratio (uPCR) < 4mg/mg and eGFR > 60 ml/min/1.73m2 using Cockcroft Gualt formula. Moderate risk included uPCR 4-8 mg/mg and eGFR > 60 ml/min/1.73 m2 and high risk as uPCR >8 mg/mg and eGFR < 60ml/min/1.73 m2. Remission was defined as > 50% reduction in proteinuria and uPCR of <3.5

mg/mg.In histopathology, based on degree of interstitial nephritis and tubular atrophy patients were categorized into three groups viz.1+ is <25%, 2+ is denotes 25%-50% and >50% as 3+.C1q staining was reported as negative,1+,2+ and 3+ depending on the intensity of staining in immunofluorescence.

STATISTICAL ANAYSIS PLAN:

For data description, continuous variables with symmetric distribution were presented as the mean ± SD. Student's t- test and analysis of variance (ANOVA single factor) were used for parametric analysis. Categorical variables were described as frequencies or percentages, and the data were analyzed with Chi-Square tests. All of the statistical analyses were conducted using SPSS, version 16.0.

RESULTS

Profile of our study population:

A total of 98 patients with biopsy proven membranous nephropathy (MN) were included in the study. Of which 5 patients who presented with end stage renal disease at presentation were excluded. Ninety three patients were included in the study. After screening for secondary causes 56/93 (60%) were diagnosed as primary MN and remaining 37/93 (40%) were secondary MN. The underlying causes of secondary MN patients were lupus nephritis (N=28), malignancy (N=3), hepatitis B virus (N=2) rheumatoid arthritis (N=1), and native drugs (N=3) (native drugs were presumed to be the etiology, considering the temporal relationship between the consumption of native drugs and onset of proteinuria) {Tab: 4}. Mean age of presentation was 39.6 years**;** 55% (51/93) of them were males. The mean serum creatinine and eGFR were 1.1 mg/dl and 73.4ml/min/1.73 m2 respectively. Mean uPCR was 4.27 mg/mg; sixty nine percent (64/93) of patients had nephrotic proteinuria; mean serum albumin was 3.2 g/dl and mean serum cholesterol was 208mg/dl.

Table.4: Spectrum of secondary MN:

s.no.	Secondary MN (Total - 31)	Percentage
1	Lupus nephritis	28(75.6%)
2	Malignancy	3(8%)
3	Drugs	3(8%)
4	Hepatitis B	2(5.4%)
5	Rheumatoid arthritis	1(2.7%)
TOTAL		37

Clinical and laboratory parameters of primary and secondary MN:

Table 5 and Table 6 show the clinical characteristics and laboratory parameters of MN patients at the time of presentation. On comparing the age distribution, most of our primary MN patients were within 40-60 years of age 55% (31/56) and most of the secondary MN group were outside this range 78% (29/37) which is statistically significant (p=0.0012). Sixty six percent (37/56) of them were males in primary MN group but in secondary MN majority of them were females 62% (23/37) which was statistically significant(p=0.007). Primary MN patients had

severe disease at the time of presentation when compared to the secondary MN patients in the form of proteinuria, serum albumin and serum cholesterol. Edema was present in significant number of patients in primary MN (p=0.016). Primary MN patients had severe proteinuria when compared to those with secondary MN (uPCR, 4.75mg/mg vs.3.60 mg/mg, p=<0.001).The serum albumin level was low in primary MN patients (3.07g/dl vs.3.49 g/dl p=<0.001) and serum cholesterol was significantly high (224 mg/dl vs. 184mg/dl p=<0.001).Significant proportion of secondary MN patients had microhematuria than those with primary MN (40.5% vs. 12.5% p=0.0018).However there was no significant difference in estimated GFR among both the groups.

TABLE.5: Clinical profile of MN.

s.no	Variables	Primary MN	Secondary MN	p value
	TOTAL	56	37	
1	Age	41.05±10.2	37.32±11.18	0.1005
2	Age in 40 to 60 yrs	31	8	0.0012
3	Male	37	14	0.007
4	Diabetes mellitus	1	3	0.141
5	Hypertension	7	7	0.396
6	Edema	41	18	0.016

Table.6: Laboratory profile of MN

s.no	Variables	primary	Secondary	p value
	TOTAL	56	37	
1	Hemoglobin (g/dl)	11.8±2.4	11.5±2.3	0.429
2	Hematuria	7	15	**0.002**
3	u PCR (mg/mg)	4.75±1.5	3.6±0.96	**<0.001**
4	Nephrotic proteinuria	42	22	0.114
5	Sr. creatinine (mg/dl)	1.12±0.38	1.23±0.93	0.414
6	e GFR (ml/min/1.73 m2)	74.5±22.8	72.2±24.9	0.640
7	Sr.albumin(g/dl)	3.07±0.62	3.49±0.47	**<0.001**
8	Sr. total cholesterol (mg/dl	224±23.6	184±47	**<0.001**
9	Random Blood sugar(mg/dl)	106.4±23.6	107±27.8	0.900

Biopsy profile of primary MN and secondary MN:

Biopsy of primary MN and secondary MN patients were compared based on C1q staining in immunofluorescence. 57 %(21/37) of secondary MN had at least 1+ C1q staining when compared to 7 %(4/56) in those with primary disease. On comparing the intensity of staining, 46 %(17/37) of secondary MN patients had **> 1+** intensity but none of the primary MN had **> 1+** staining. {Tab: 7}

Table.7: Histopathology of MN: (C1q staining in IF only)

Variable		Primary MN	Secondary MN	p value
C1q Staining	0	52	16	**0.049**
	1+	4	4	
	2+	0	9	
	3+	0	8	
Total **93**		**56**	**37**	

IF – Immunofluorescence.

Analysis of remission rate of primary MN:

To assess the correlation between the initial clinical presentation and remission rate, we followed up all the idiopathic MN patients. Secondary MN patients were excluded from the analysis as the remission depends on the underlying cause. Median follow up period was 18 months (6 - 24 months). All the study subjects received RAAS (rennin angiotensin aldosterone system) inhibitors. Immunosuppressive therapy was started in indicated patients as per KDIGO guidelines. Out of 56 primary MN patients, 33 (59%) received the modified Ponticelli (m.P) regimen. Strict adherence to the regimen was ensured. Remaining 23 patients had not received immunosuppressive therapy. Fourteen of them were under mild risk category hence immunosuppressant drugs were not indicated at that time. They were treated conservatively with RAAS inhibitors and other

supportive drugs. Among the remaining 9 patients, three discontinued the regimen due to serious infections, three were non compliant to the regimen, two were not willing for any treatment and one was started on calcineurin inhibitor based regimen as she was planning to become pregnant in near future . All the patients were on regular follow up**.** Out of 56 primary MN patients, 30 % (17/56) of patients achieved remission. Out of 33 patients who received modified Ponticelli regimen 24 % (8/33) achieved remission. Spontaneous remission occurred in 9 out of these 14 patients (64%) who were under conservative therapy**.** There is no statistical significance of remission in both the group (p=0.67) {Table.8}.

Table.8: Remission and modified Ponticelli regimen.

	Received m.P	Not received m.P	Total	p value
Remission achieved	**8**	**9**	**17**	**0.670**
Remission not achieved	**25**	**14**	**39**	
Total	**33**	**23**	**56**	

Adverse effects during modified Ponticelli regimen:

Gastrointestinal infection occurred in 2 patients, lower respiratory infection in 3, drug induced DM in one patient and allergic reaction in one patient. All these patients recovered completely after receiving appropriate treatment.

Correlation between the initial clinical presentation and remission rate in primary MN:

We tried to analyze whether the clinical or laboratory parameter at the time of initial presentation predicts remission in primary MN patients. Patients having severe disease at the time of presentation had poor remission rate (both in conservative and immunosuppressive therapy) when compared to that with mild disease. Patients who had not remitted had severe proteinuria (uPCR 5.3 mg/mg vs. 3.3 mg/mg p=<0.001).Also serum albumin in them was significantly lower (2.8 g/dl vs. 3.47 g/dl p=<0.001) and serum cholesterol was significantly high (241mg/dl vs.184mg/dl p=0.0017).But creatinine clearance showed no significant difference between the groups (72.41 ml/min/1.73m2 vs.79.9 ml/min/1.73m2).{Table.9 & 10}

Table.9: Initial clinical presentation and remission.

s.no	Variables	Remission present	Remission absent	p value
	TOTAL	17	39	
1	Age	39.8±8.3	41.59±11	0.557
2	Male	11	26	0.877
3	Diabetes mellitus	1	0	0.125
4	Hypertension	3	4	0.439
5	Edema	10	31	0.107

Table.10: Initial laboratory parameters and remission.

s.no	**Variables**	Remission present	Remission absent	p value
	TOTAL	17	39	
1	Hemoglobin (g/dl)	12.7±1.94	11.5±2.58	0.104
2	Hematuria	3	4	0.440
3	u PCR (mg/mg)	3.31±1.35	5.33±1.22	**<0.001**
4	Nephrotic proteinuria	5	37	**<0.001**
5	Sr. creatinine (mg/dl)	1.12±0.38	1.03±0.29	0.352
6	e GFR (ml/min/1.73 m2)	72.2±21.1	79.98±22.6	0.246
7	Sr.albumin(g/dl)	3.47±0.47	2.80±0.57	**<0.001**
8	Sr. total cholesterol (mg/dl	184.2±26.3	241.8±69.4	**0.0017**
9	Random Blood sugar(mg/dl)	103±25.06	107.9±23	0.481
10	Immunosuppressant drugs	8	9	0.670

Histopathology of initial biopsy and remission in primary MN.

In order to assess the correlation between the histopathological features of initial biopsy of the kidney and the remission among primary MN patients, we compared the degree of interstitial fibrosis of those achieved remission and those who had not remitted. Out of 17 patients who achieved remission, 59% (10/17) had no interstitial fibrosis and tubular atrophy and out of 39 patients who had no remission 60% (23/39) had no interstitial fibrosis and tubular atrophy. None of the patients who achieved remission had severe interstitial fibrosis and tubular atrophy (> 50%) and 13% (5/39) of those who had no remission had severe interstitial fibrosis and tubular atrophy .Though severe interstitial fibrosis and tubular atrophy was more with those who had not achieved remission this could not statistical significance.{Table.11}

Table.11: Histopathology and remission in primary MN.

(Compared only interstitial fibrosis and tubular atrophy in light microscope.)

Variables		Remission present	Remission absent	p value
Interstitial fibrosis & Tubular atrophy	0	10	23	**0.439**
	1+	5	11	
	2+	2	0	
	3+	0	5	
TOTAL (56)		17	39	

Comparison of variables between CKD and stable renal function.

In order to evaluate whether the initial clinical, laboratory and histopathological parameters could predict the progression of renal failure, we compared these variables between those who had stable renal function and those progress to renal failure. During the follow up of 56 primary MN patients, 10 % (6/56) of them developed progressive renal failure. Out of the 6 patients who progressed to renal failure, 67% (4/6) had interstitial fibrosis and tubular atrophy of >25% when compared to 6% (3/50) in those who had stable renal function. Hence those patients having severe interstitial fibrosis and tubular atrophy (> 25 %) at the time of presentation progressed to renal failure during the follow up period. Five out of 6 (83%) patients progressing to renal failure had nephrotic proteinuria as compared to 37 out of 50 patients (74%) having stable renal function. One patient among the group progressed to renal failure had remission (16%) as compared to 16 out of 50 (32%) in stable renal function group. Though statistically not significant, proportion of patients having nephrotic proteinuria and reduced remission rate had high probability for progressing to renal failure.{Table.12}

Table.12: Comparison of variables between CKD and stable renal function.

s.no	Variables	CKD present	Stable renal function	p value
	TOTAL	6	50	
1	Age	43.3±11.6	40.7±10.1	0.56
2	Male	5	22	0.34
3	Hypertension	0	7	0.32
4	Hemoglobin (g/dl)	10.4±2.9	12±2.3	0.13
5	Hematuria	3	4	0.003
6	u PCR (mg/mg)	5.06±1.8	4.67±1.5	0.578
7	Nephrotic proteinuria	5	37	0.617
8	Sr. creatinine (mg/dl)	1.6±0.59	1.1±0.35	0.386
9	e GFR (ml/min/1.73 m2)	74.3±30.5	74.6±22	0.605
10	Sr.albumin(g/dl)	0.61	3.03±0.62	0.353
11	Sr. total cholesterol (mg/dl	275±88.7	218±60	0.041
12	Random Blood sugar(mg/dl)	113±39.94	105.6±21.38	0.434
13	Severe interstitial fibrosis &tubular atrophy (>25%)	4	3	<0.001
14	Remission	1	16	0.439

Fig.1: Spectrum of membranous nephropathy. (Total 93)

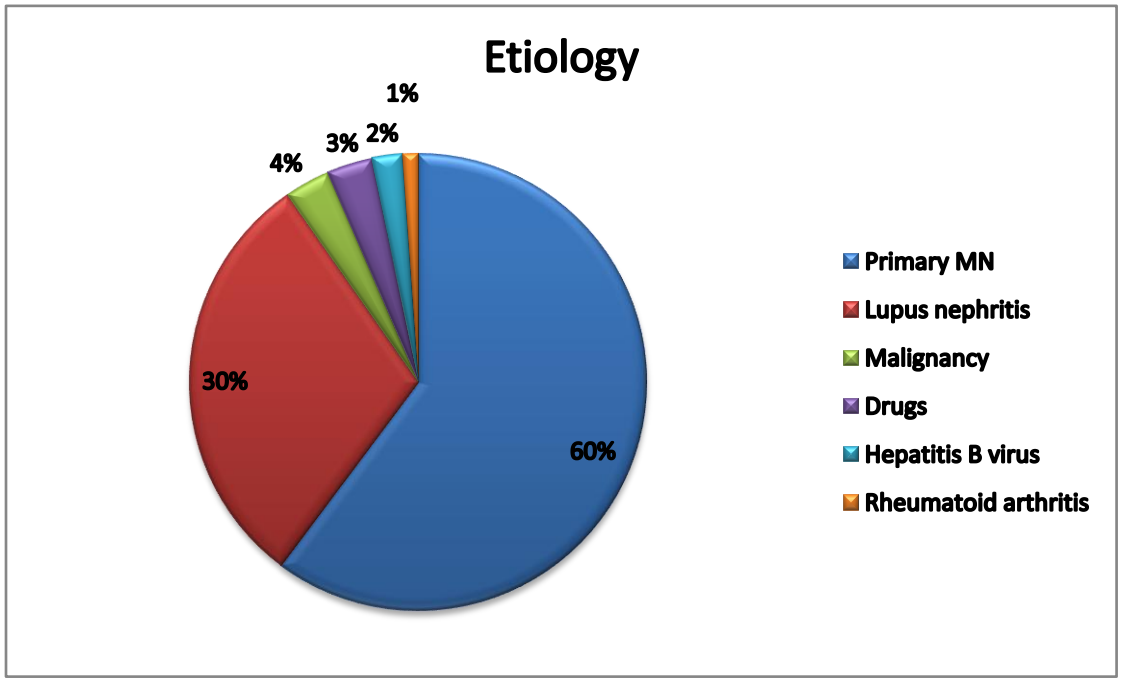


Fig.2: Sex ratio.

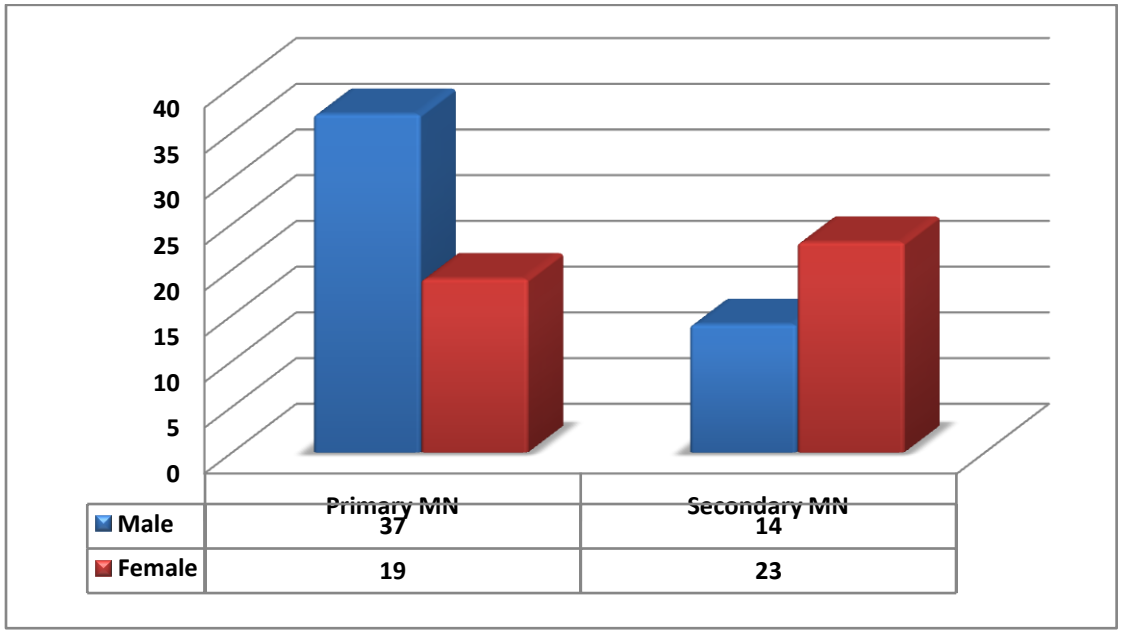


Fig.3: **Clinical features of statistical significance at the time of presentation.**

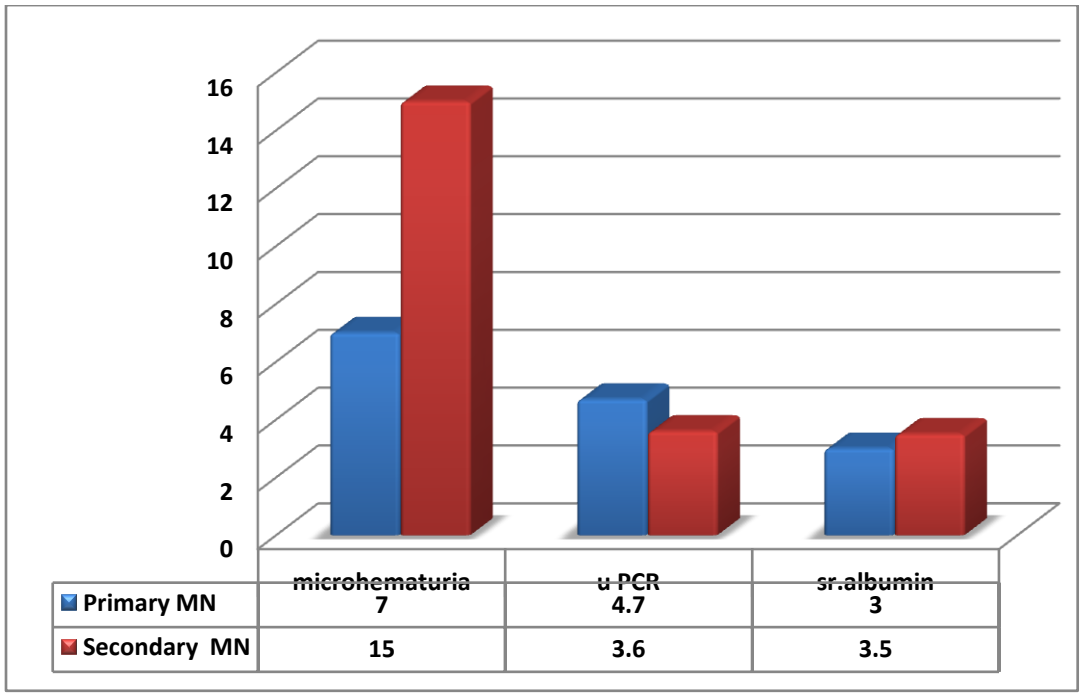


Fig.4: **C1q staining in primary and secondary MN**

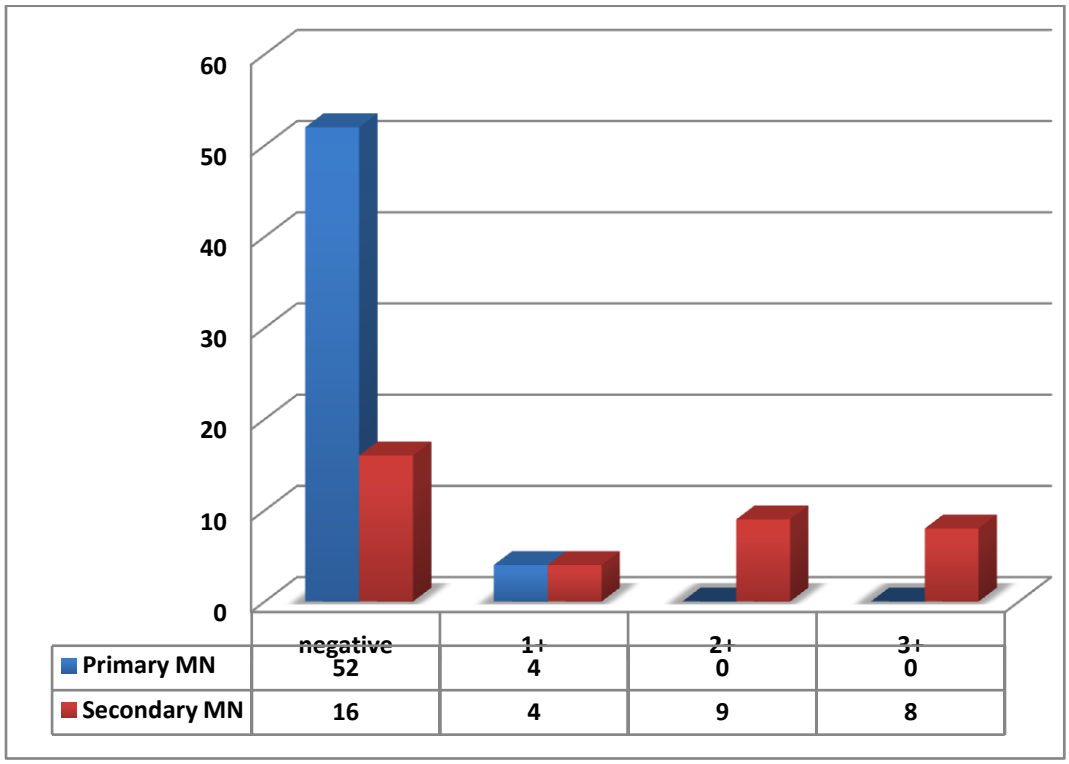


Fig.5: Clinical features at the initial presentation and remission

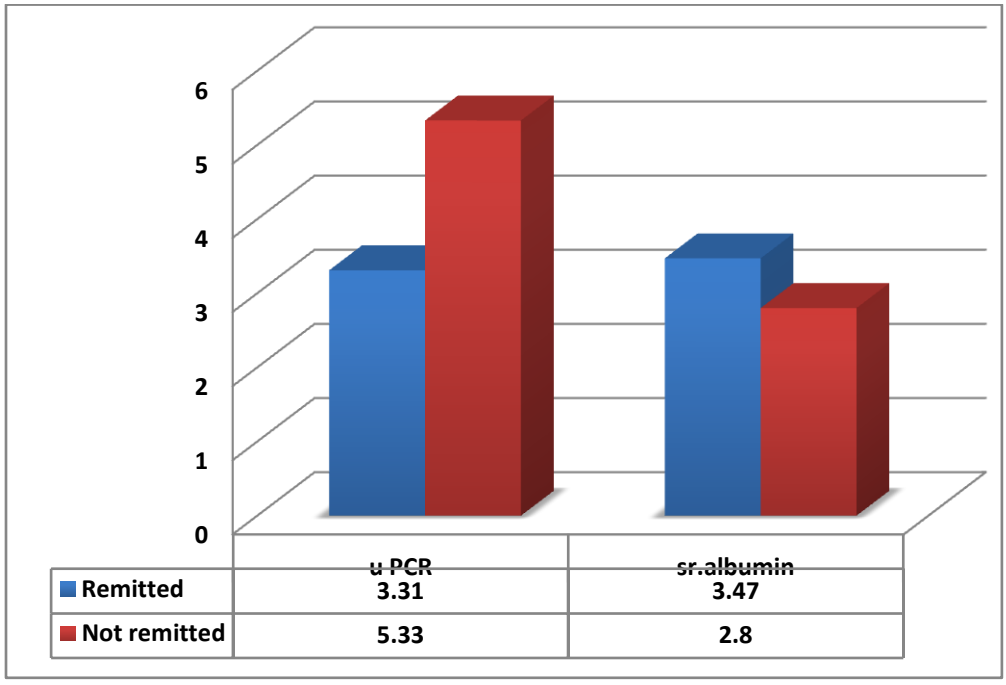


Fig.6: **Outcome after modified Ponticelli regimen**.

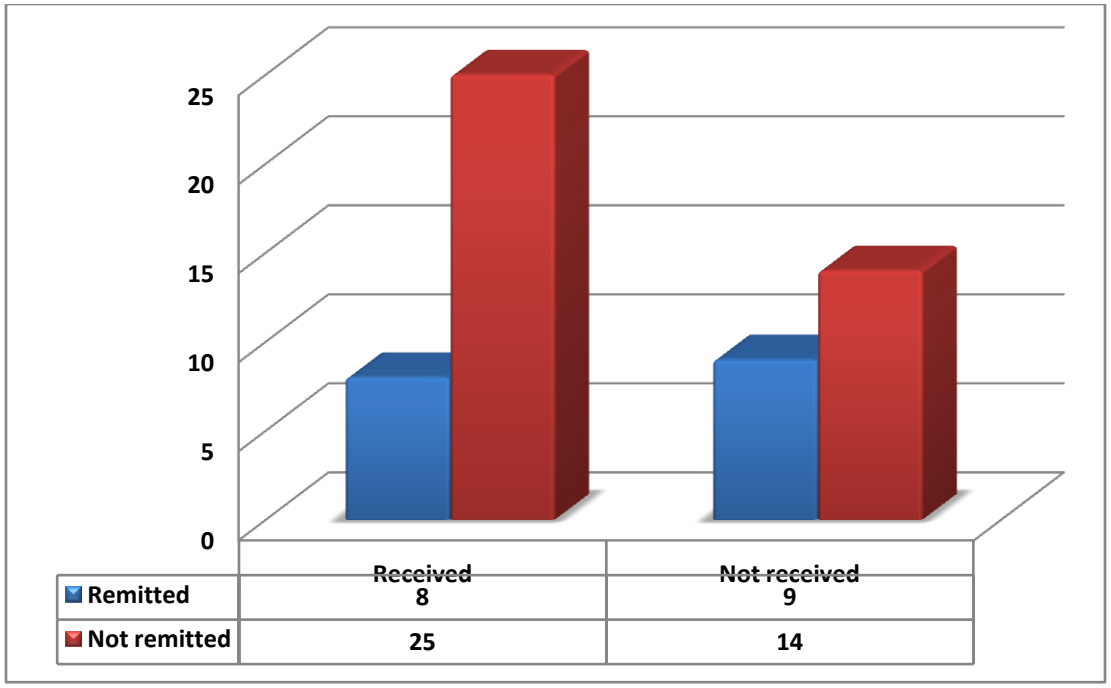


Fig.7: **Histology and CKD progression**

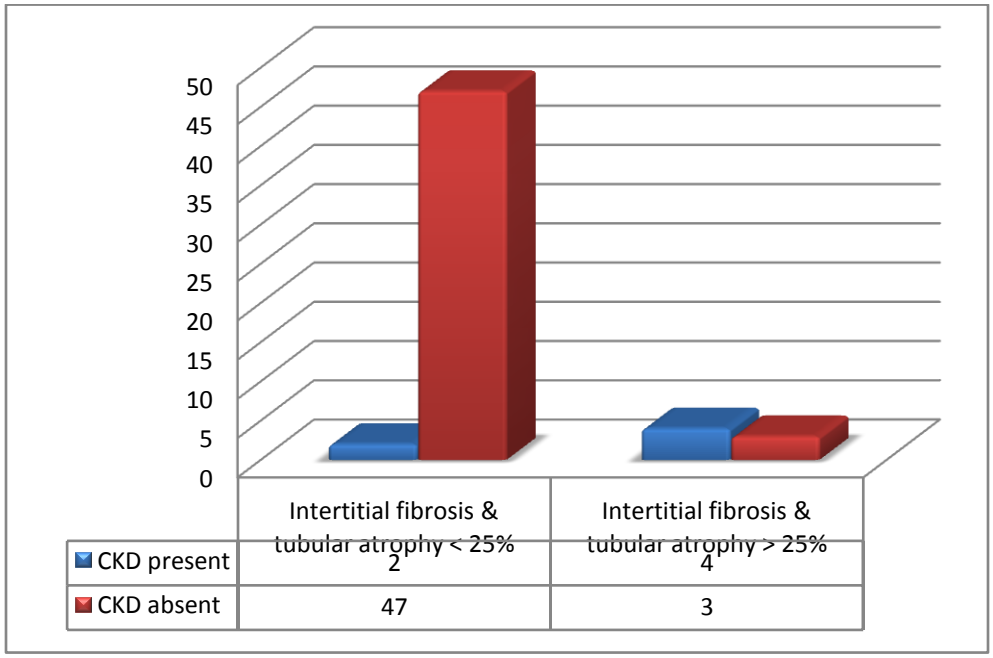
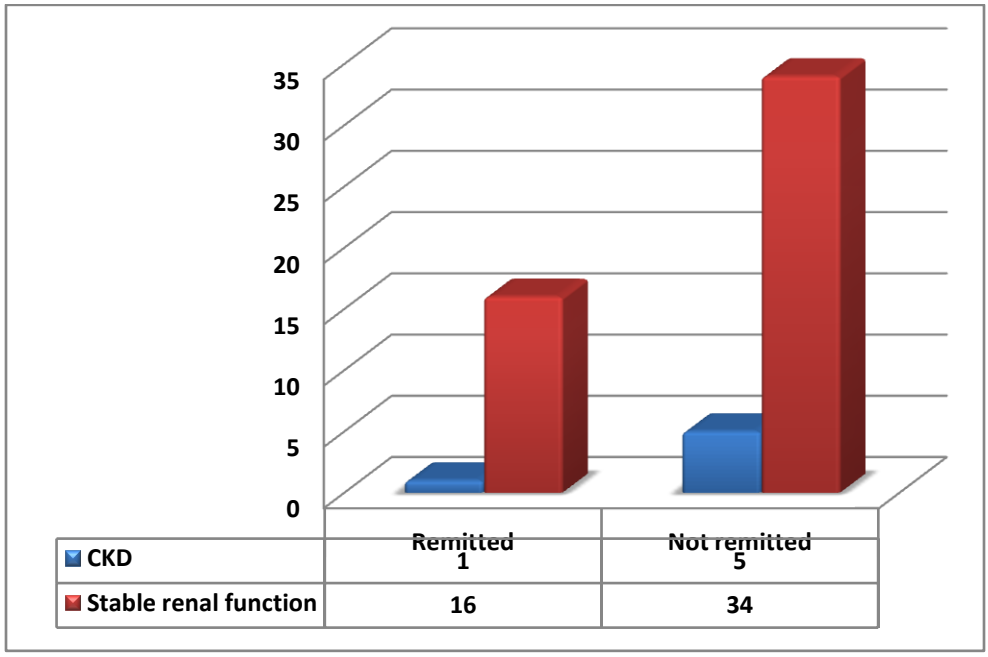


Fig.8: **Remission and CKD progression**



DISCUSSION

In our study 60% of study population were idiopathic MN and 40% were secondary MN supporting the fact that primary is more common than the secondary MN .Among the secondary MN, lupus nephritis was constituting the most, of 75.6% of cases. Sixty six percent (37/56) of primary MN patients were males and majority of the secondary MN were females accounting for 62% (23/37). Hence, females are more likely to have secondary MN as compared to male. But in our study, lupus nephritis was the major contributor of secondary MN, accounting for 75% which is more common in females.

On analyzing the age, as per previous studies, usual age of presentation of primary MN is in the fourth and fifth decade. In our study also, 55% (31/56) of primary MN patients were within the range of 40-60 years of age. But among the secondary MN patients, 78% (29/37) was outside this range which was statistically significant. This shows that patients presenting outside the usual range of 40-60 years more likely to have secondary MN**.**

Primary MN patients had severe disease in our study. Pedal edema was more common among primary MN than in secondary MN. Also, proteinuria, hypoalbuminemia and hypercholesterolemia were severe among the primary MN patients. Seventy five percent of patients in primary MN presented with nephrotic

proteinuria. Forty percent (15/37) of patients presented with microhematuria among the secondary MN group as compared to 12% (7/56) in primary MN group. Though microhematuria can occur to a maximum of 50% in patients with primary MN, our study suggests screening for secondary cause before concluding these patients as primary. Patients having severe disease are more likely to have primary MN. However, there was no significant difference in the creatinine clearance between the two groups at the time of presentation.

Immunofluorescence staining of primary MN is usually IgG and C3. Studies show that staining for other deposits like C1q suggests secondary MN. Our study also confirms this notion. Fifty eight percent (21/37) of secondary MN in our study had positive for C1q staining as compared to be 7% (4/56) in primary MN patients which is significant statistically(p=). Also, the intensity of staining is more in secondary than in the primary MN. Forty six percent (17/37) of secondary MN had more than 1+ staining for C1q as compared to none in the primary MN patients. Intense C1q staining in the histopathology of kidney biopsy in MN patient suggests secondary form of MN.

Among the total 56 primary MN patients, 30.5% (17/56) achieved remission. Though our study was not designed for assessing the effectiveness of

the disease specific therapy (modified Ponticelli regimen), we compared the rate of remission in those patients who received this therapy and those treated conservatively. The modified Ponticelli regimen included 6 months therapy of steroid and oral cyclophophamide on alternate months. Remission was achieved in 24% (8/33) of patients immediately after completing the regimen. Forty percent (9/23) of remaining 23 patients on conservative treatment had remission.

Various studies have shown that remission can occur even months after completion of this regimen. KDIGO also holds the view that, it is reasonable to wait for 12 -18 months after the immunosuppressive therapy before concluding that initial therapy has been ineffective. At this juncture it would be worth mention the role of Apla2r in assessing the remission .Studies showed that in primary MN patients, anti APL2R antibody starts reducing and disappear (immunological remission) much earlier than that of remission of proteinuria (clinical remission).This would prevent unwarranted exposure of patients to these toxic immunosuppressant drugs . But it is rather intriguing to address the question – would it be justified to tailor immune therapy according to the immunological reactivity. Randomized controlled trials are need for answering this question.

Our study also demonstrated that patients having severe disease had lesser chance of remission when compared to milder category. Proteinuria, hypoalbuminemia and hypercholesterolemia had inverse relationship to the rate of

remission (conservative and immunosuppressive therapy combined).There is no difference in creatinine clearance among the two groups. The small sample size of this subcategory has made the analysis difficult. However, apparently there exists good correlation between the severity of disease and low creatinine clearance at the time of presentation and rate of remission.

Our study also confirms the previous notion that degree of interstitial fibrosis and tubular atrophy in the biopsy done at the time of initial presentation do not have an influence over rate remission.

As we know that one third of patients will progress to renal impairment, it is essential to identify such high risk patients at the time of presentation enabling them to start on intense therapy. This will avoid unnecessary exposure of toxic drugs to the remaining two third of patients. Degree of proteinuria and urinary level of C5-9 and β 2 microglobulin and serum creatinine were used by few authors for risk stratification. We tried to analysis the epidemiological, clinical, biochemical and histopathological parameters as predictors of progression to renal impairment.

In our observation, 10% (6/56) of primary MN patients progressed to chronic renal disease in our population. Presence of interstitial fibrosis and tubular atrophy of >20% in the biopsy done at the initial time of presentation, was good

predictor for progression to chronic renal disease in our study population. Progression to chronic kidney disease was more with those patients having proteinuria of > 3.5 mg/mg creatinine and those who had not remit either by conservative or by immunosuppressive drugs though it was not statistically significant. We could not achieve significance statistically as the sample size of subcategory is very small.

Limitations:

There are few limitations in our study. Our study group is of limited size. Study is as a prospective single centre observational study. Patients were followed up for a short period. Remission of proteinuria was assessed immediately after completing the modified Ponticelli regimen. Patients not remitted during this study may remit after the study period. We could not assess the APLA2R activity for study population which would further support our differentiation into primary and secondary MN.

Conclusion

- Primary MN was more common than secondary MN in our study accounting for about 60%.

- On comparing the variables, the observations were as follows.

  i) Age:

  - Primary MN was common in between 40-60 years
  - Secondary MN was outside this range

  ii) Sex:

  - Males were common in primary MN
  - Females were common in secondary MN.

  iii) Primary MN had severe disease at the time of presentation in the form of

  - Presence of edema, severe proteinuria, hypoalbuminemia and hypercholesterolemia

  iv) C1q staining in the biopsy was more common in secondary MN.

Though the type of MN may be suspected to some extent by these clinical, biochemical and pathological features, they individually cannot differentiate primary from secondary MN. Combining all these parameters along with the search for secondary causes and detection of APLA2R antibody will help in this regard.

- Remission is less likely in patients having severe disease at the time of presentation. The degree of interstitial fibrosis and tubular atrophy has no effect on remission in these patients.

- Interstitial fibrosis and tubular atrophy of >25% in the initial biopsy picture is a definite risk factor for progression to renal impairment. Patients with nephrotic proteinuria and those who do not remit have higher chance for progression to chronic kidney disease.

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PROFORMA

Name: Age: Sex: MRD: NC No: Date:

Phone No: Native: Wt: Ht: BMI:

Presenting compliance	YES/NO	Duration
Edema		
Oliguria		
Frothy urine		
Hematuria		
Diabetes mellitus		
Hypertension		
Joint pain , skin rashes ,oral ulcers,		
Jaundice , Blood transfusion		
Weight loss, treatment for malignancy		
Native drugs , analgesic drug intake		

Examination: Blood pressure: Pulse rate:

C.V.S.: R.S: P/A: C.N.S:

Biopsy report:

Variable	Nil	1+	2+	3+
Interstitial fibrosis & tubular atrophy				
C1q staining				

Follow up: Y / N Duration of follow up:

Laboratory parameters:

Parameters	At presentation	3 months	6 months	Last follow up
Urine Protein				
24 h urine pr / uPCR				
Urine RBC				
Hemoglobin				
Sr. Urea				
Sr. Creatinine				
eGFR				
Sr. Total protein				
Sr. Albumin				
Sr. Cholesterol				
Antinuclear antibody				
Hepatitis B surface antigen				
Anti hepatitis C antibody				
H.I.V				
Stool for occult blood				
Upper G.I. Endoscope				
X ray chest				
C.T. thorax				
Mammography				
Prostate specific antibody				

Treatment	**Drugs**	**Duration**
Immunosuppressant drugs		
Supportive treatment		

CONSENT FORM

TITLE OF PROJECT:

CLINICAL PROFILE, CLINICOPATHOLOGICAL CORRELATION & OUTCOME OF ADULT MEMBRANOUS NEPHROPATHY

Name of Researcher: **Dr.ABEESH. P**

Please tick to confirm

I confirm that I have read and understand the information provided to me for the above study.	☐
I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐
I agree to take part in the above research study.	☐

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of Person taking consent (if different from researcher)	Date	Signature
_____	_____	_____
Researcher _____	Date	Signature

PRIMARY MN

FINAL MASTER CHART

S.NO	NAME	AGE	sex	WT	EDEMA	DM	HT	RBC	uPCR I	u PCR >3.5	HB	CR I	e GFR	T.PROTEIN	ALBUMIN	CHOLESTRC	BL.SUGAR	ANA	C3	C4	ANTI ds D	MOTION O
1	ALBERT	34	M	45	N	N	N	N	2.3	N	13.8	0.9	73.6	5.9	3.1	186	98	NA	NA	NA	NA	N
2	BHUVANES	41	F	43	N	N	N	N	2.4	N	13.2	1	59.1	5	3	189	95	N	NA	NA	NA	N
3	GEETHA	40	M	66	Y	N	Y	N	2.4	N	9	1.9	48.2	5.9	4.1	200	128	N	N	N	N	N
4	MALAR	45	F	39	N	N	N	N	3.16	N	14	0.9	59.2	4.9	3.8	168	98	N	N	N	N	N
5	MALLIGA	44	F	55	Y	N	N	N	2.7	N	14.8	0.9	69.3	5.6	3.2	172	110	N	NA	NA	NA	N
6	MURUGAN	40	M	65	Y	N	N	Y	3.7	Y	13.5	2.1	43	5.7	3.5	170	110	NA	NA	NA	NA	N
7	NAGARAJ	56	M	54	Y	N	Y	N	3.1	N	11.8	1.3	48.5	6.6	3.8	196	64	N	NA	NA	NA	N
8	NOORLAM	36	M	39	N	N	N	N	3.2	N	10.9	0.8	106.5	6.2	3	210	98	NA	NA	NA	NA	N
9	PUSHPA	32	F	56	Y	N	N	Y	2.9	N	10.8	0.8	89.3	6.4	3.2	169	90	NA	NA	NA	NA	N
10	RAMALING	43	M	53	Y	N	N	N	1.65	N	13.9	0.8	93	5.7	3.3	210	96	N	NA	NA	NA	N
11	SAMPATH	30	M	66	N	N	N	Y	3.1	N	15.4	1.2	72	3.7	2.8	180	95	N	NA	NA	NA	N
12	SATHYA	30	F	58	N	N	N	N	3.8	Y	13	0.9	83.3	5.6	3.9	187	130	N	N	N	N	N
13	SELVAN	49	M	51	N	N	N	N	2.96	N	14.8	1.1	58.6	6	4	145	90	N	NA	NA	NA	N
14	SENTHIL.B	32	M	71	Y	N	N	N	4	Y	13.8	1	106	6.2	4	234	86	N	NA	NA	NA	N
15	SURENDRA	51	M	77	Y	Y	N	N	3.1	N	12.6	0.9	105	4.8	2.9	198	180	N	N	N	N	N
16	SURESH G	27	M	53	Y	N	N	N	8	Y	11.2	1.5	55.5	4.2	4.2	198	88	N	N	N	N	N
17	THILLAIRAI	47	F	65	Y	N	Y	N	3.85	Y	8.9	1	61	6	3.2	120	96	NA	NA	NA	NA	N
18	ALAGARSA	33	M	59	Y	N	N	N	6.4	Y	12	0.9	97.4	5.9	2.1	252	96	N	NA	NA	NA	N
19	BABU	37	M	44	Y	N	N	N	6.7	Y	9	1.1	57.2	5.6	2.2	225	110	N	N	N	N	N
20	DESAPPAN	53	M	55	Y	N	Y	N	6.3	Y	10.4	1.2	55.4	6.3	2	201	90	N	NA	NA	NA	N
21	DEVASIGAI	52	M	65	N	N	N	Y	4.3	Y	5.2	4.5	66.2	6.7	1.9	220	64	NA	NA	NA	NA	N
22	DEVI	31	F	56	Y	N	N	N	5.9	Y	10.8	0.8	90.1	4.8	2.3	228	120	N	N	N	NA	N
23	DHANALAK	33	F	43	N	N	N	N	4.5	Y	12.8	1.1	49.4	5.8	2.1	210	180	N	N	N	N	N
24	ELANGOVA	52	M	65	Y	N	N	N	3.52	Y	13.8	0.9	75	6	1.8	240	142	NA	NA	NA	NA	N
25	GUNASEKA	41	M	73	Y	N	Y	N	5.1	Y	10.2	1.4	71.7	6.9	3.2	210	120	N	N	N	N	N
26	INDRA	47	F	45	Y	N	N	N	7.4	Y	9.2	0.9	68.9	5.6	3.1	290	110	N	N	N	N	N
27	JEEVARATH	30	M	39	Y	N	N	N	6.6	Y	13.8	0.8	63.3	5.9	2.8	218	94	NA	NA	NA	NA	N
28	JEYAKUMA	40	M	49	Y	N	N	N	8.2	Y	12.1	1.2	56.7	3.8	2.4	330	130	N	N	N	N	N
29	JOSEPH	50	M	55	Y	N	N	N	4.1	Y	15.4	1	68.8	6.7	2.6	210	90	NA	NA	NA	NA	N
30	KASTHURI	42	F	67	Y	N	N	N	7.4	Y	10.8	0.7	101.3	5.6	2.2	370	90	N	NA	NA	NA	N
31	KUPPUSAM	38	M	69	N	N	N	N	5.13	Y	12.8	1	83.3	5.9	3	198	110	N	NA	NA	NA	N
32	MAHALING	52	M	45	Y	N	N	N	5.06	Y	12	0.9	61.1	6.5	3.2	223	96	N	N	N	N	N
33	MURUGAN	45	M	76	Y	N	N	N	5.14	Y	14.8	0.9	94.7	5.6	3.1	225	110	N	N	N	N	N
34	PACHAIAM	44	F	81	Y	N	N	N	6.2	Y	12	0.9	120	4.8	3.2	268	110	N	N	N	N	N
35	PARTHIBAN	28	M	70	N	N	N	N	5.7	Y	9.2	0.9	121	5.8	3.5	235	120	N	N	N	N	N
36	PARVEEN	30	F	68	Y	N	N	N	5.9	Y	12.8	0.9	98.1	5.8	3.1	190	110	N	N	N	N	N
37	POONGOD	44	F	44	Y	N	Y	N	4.5	Y	12.8	0.9	55.4	7	2	220	94	N	N	N	NA	N
38	PUSHPARA	54	M	65	Y	N	N	N	4.16	Y	13.2	1.3	59.7	4.8	3.2	418	98	N	N	N	N	N
39	RAGHU	31	M	66	Y	N	N	Y	6.4	Y	13.8	1.2	83.3	5.8	3.4	260	88	N	N	N	N	N
40	RAJESH KU	22	M	72	Y	N	N	Y	5.1	Y	12.8	0.9	131.1	5.9	3.7	310	90	N	N	N	N	N
41	RASHIDA	63	F	45	Y	N	N	N	5.78	Y	11.8	1.1	53.7	4.8	2.8	280	120	N	N	N	N	N
42	SABEENA	23	F	67	Y	N	N	N	5.8	Y	11.4	1.4	66.1	7.5	2.7	138	84	N	NA	NA	NA	N
43	SANGEETH	24	F	67	Y	N	N	N	6.25	Y	11.8	0.9	101.9	6.2	3.4	289	95	N	N	N	N	N
44	SEENI	62	M	59	Y	N	N	N	3.16	N	15	0.8	79.9	4	1.8	110	98	N	N	N	N	N
45	SEKAR	48	M	60	Y	N	N	N	2.3	N	11	0.9	85.2	5.3	2.9	281	120	N	N	N	N	N
46	SIVADASAN	54	M	64	Y	N	N	Y	5.1	Y	12.1	0.9	84.9	4.8	2.5	280	180	NA	NA	NA	NA	N
47	SUBRAMAI	56	M	69	Y	N	N	N	5.7	Y	0.8	0.9	89.4	6.8	3	214	95	N	N	N	NA	N
48	SURESH.C	25	M	54	N	N	N	N	4.9	Y	10.8	0.85	101.5	5.9	3.2	213	95	N	NA	NA	NA	N

49	VARADHAF	54	M	67	N	N	Y	N	4.1	Y	12	0.8	100	6.1	2.1	208	140	N	N	N	NEG	N
50	VIJAYA	40	F	68	N	N	N	N	3.6	Y	11.3	1	94.4	5	3.2	206	125	N	N	N	N	N
51	VISALATCH	30	F	66	Y	N	N	N	5.8	Y	14	0.9	112	5.5	3.8	216	98	N	N	N	NA	N
52	RAMALING	48	M	46	Y	N	N	N	4.6	Y	11	0.9	65.3	5.6	3.2	204	112	N	N	N	NA	N
53	MANOHAR	36	M	57	Y	N	N	N	4.3	Y	10	1.1	74.3	5.5	3.4	210	102	N	N	N	NA	N
54	RAVI	45	M	49	Y	N	N	N	5.8	Y	11.3	1.2	53.9	5.8	3.5	180	98	N	N	N	NA	N
55	SHEELA	38	F	71	Y	N	N	N	6.3	Y	11	1	100.6	6.2	3.2	480	97	N	N	N	NA	N
56	REHMAN	47	M	55	N	N	N	N	4.8	Y	12	1.2	59.2	6.7	2.6	170	89	N	N	N	N	N

SECONDARY

S.NO	NAME	AGE	sex	WEIGHT	EDEMA	DM	HT	RBC	uPCR I	uPCR >3.5	HB	CR I	e GFR	T.PROTEIN	ALBUMIN	CHOLESTRC	BL.SUGAR	ANA	C3	C4	ANTI ds D	MOTION O
57	ANAPOOR/	28	F	40	N	Y	N	N	3.9	Y	13	1.2	66.5	5.6	3	260	110	N	NA	NA	NA	N
58	ANJALI	23	F	36	N	N	N	Y	2.1	N	13	0.8	83.6	6.5	3	231	98	N	NA	NA	NA	N
59	BARANI	37	F	55	N	N	N	N	5	Y	13.8	1.5	46.4	6.4	3.5	180	80	NA	NA	NA	NA	N
60	BARATHY	37	F	54	N	N	Y	N	3.9	Y	12.3	1	60.7	6.5	3.6	240	89	N	N	N	NA	N
61	DEVI	22	F	46	N	N	N	N	2.3	N	9.2	1	80.1	5.9	3.5	150	140	POS	L	L	POS	N
62	KALAVATH	38	F	56	Y	N	N	N	6	Y	13.7	1.3	62.9	6.4	3.4	212	98	N	NA	NA	N	N
63	KAMALAVE	32	F	57	N	Y	Y	N	4.3	Y	8.7	1.6	42.3	6.5	3.5	128	78	POS	L	L	NA	N
64	KUMUTHA	23	F	58	N	N	N	Y	3.8	Y	9	1.3	55	6	4	210	89	POS	NA	NA	NA	N
65	LAKSHMI	48	F	61	Y	N	N	N	3.8	Y	9.5	1.2	57.6	5.9	3.2	220	112	NA	NA	NA	NA	N
66	PADMA	35	F	58	N	N	Y	N	3.06	N	7.7	0.7	85.4	6.1	3.6	290	180	POS	N	N	NA	N
67	RAJESWAR	30	F	46	Y	N	Y	Y	4.2	Y	11.5	1.2	76.5	5.5	2.9	280	98	POS	NA	NA	NA	N
68	SELVARANI	33	F	51	N	N	N	N	2.7	N	12.6	1.1	65.4	5.8	3.2	190	110	NEG	N	N	N	N
69	SELVI	47	F	60	Y	N	N	Y	4.5	Y	11.8	0.8	77.9	6.8	3.2	140	92	NA	NA	NA	NA	N
70	SHANTHI	40	F	56	N	N	N	N	2.07	N	10.8	0.9	55.3	6	3.3	190	108	N	NA	NA	NA	N
71	TAMIL SELV	30	F	48	N	N	Y	N	3.7	Y	12.6	0.9	66.9	4.5	3.2	180	140	POS	N	N	N	N
72	TAMILSELV	28	F	49	N	N	N	Y	2.1	N	8.5	1	65.7	6	4.8	120	98	N	L	L	NA	N
73	THILAGAV/	38	F	50	Y	N	N	N	4.2	Y	7.5	1.6	45.1	4.8	4	160	110	POS	N	N	N	N
74	UMASELVI	37	F	59	Y	N	N	Y	4.6	Y	15.8	1	52.1	6.5	3.2	115	220	NEG	NA	NA	NA	N
75	VANI	39	F	60	Y	N	N	Y	4.7	Y	16.2	1	66.3	5.4	4.9	120	64	NA	NA	NA	NA	POS
76	RAJESWAR	50	F	55	Y	N	Y	N	4.2	Y	11.2	0.8	130.7	5.6	3.2	179	120	N	NA	NA	NA	N
77	NATHYA	25	F	52	N	N	N	Y	2.2	N	5.8	1.8	47.2	5.4	2.8	254	76	NA	NA	NA	NA	N
78	SATHYA	35	F	49	N	N	N	Y	3.2	N	12	0.9	73.2	4.9	3.5	236	100	POS	N	N	N	N
79	SASIKALA	35	F	50	N	N	N	N	2.5	N	8.2	1	66.3	5.8	3.8	121	120	N	N	N	N	N
80	BALARAM/	69	M	62	Y	N	N	N	3.2	N	10.5	0.9	73.5	5.4	3.8	215	98	NA	NA	NA	NA	N
81	GOWTHAM	24	M	67	Y	N	N	Y	3.4	N	13	1.6	40.5	5.8	3.2	190	94	POS	NA	NA	POS	N
82	KANNAN	39	M	72	Y	N	N	Y	3.75	Y	12	1.1	65.2	5.6	3.7	140	98	POS	NA	NA	NA	N
83	KARTHIK	25	M	77	N	N	N	Y	4.1	Y	10.2	1.2	43.3	4.5	3.2	192	120	POS	L	L	NA	N
84	KUMAR	41	M	65	N	N	N	Y	4	Y	12.5	0.8	77.5	6.8	4.1	128	110	N	NA	NA	NA	N
85	MARIO	33	M	66	Y	N	N	N	2.1	N	10.8	0.9	71.2	5.7	4	136	98	POS	NA	NA	NA	N
86	PRAKASH	35	M	76	Y	N	N	N	4.6	Y	12	0.8	76.1	6.3	3.6	173	96	NEG	NA	NA	NA	N
87	SURESH P	34	M	61	Y	N	N	N	3.85	Y	11.8	0.9	78.4	5.5	3	205	95	N	N	N	NA	N
88	THIRUPATH	30	M	48	Y	N	N	N	2.1	N	10.3	1.1	61.3	5.6	3.7	185	98	POS	L	L	NA	N
89	ALPHONES	64	M	58	Y	Y	N	Y	4.3	Y	13.8	0.8	117.8	4.2	3	213	120	N	N	N	N	N
90	BHESEER	54	M	60	Y	N	Y	N	4.2	Y	13.8	0.9	84.4	5.2	3.9	180	89	POS	N	N	NA	N
91	MOHAN	36	M	54	Y	N	N	N	4.4	Y	13.8	0.9	84.8	6	3.3	160	110	POS	NA	NA	NA	N
92	PONNAN	57	M	71	N	N	N	Y	3.1	N	12.3	0.5	128.3	6.3	3	160	98	NEG	N	N	N	N
93	KANNAN	50	M	77	N	N	N	N	3.3	N	12.9	0.7	89	6.1	3.5	125	110	POS	N	N	N	N

FINAL MASTER CHART

HBSAG	ANTIHCV	HIV	PSA	CT THORA)	OGD	،MMOGRAF	APLA2R	IFTA	IGG	IGM	IGA	C3c	C1Q	ACEI/ARB	M. P	REMISION		CR II	e GFR	uPCR II	ALBUMIN II
N	N	N	N	NIL	NIL		POS	1	2+	1+	1+	2+	0	Y	Y	Y	1	0.9	73.6	2.9	3.9
N	N	N		NIL	NIL	N	NA	1	2+	1+	0	1+	0	Y	N	Y	1	0.9	61	1.6	4.2
N	N	N	N	NIL	NIL		NA	0	2+	0	0	2+	0	Y	Y	Y	1	1.2	64	1.3	4.3
N	N	N	N	NIL	NIL	N	NA	0	4+	0	2+	2+	0	Y	N	Y	1	0.9	59.2	1.4	3.9
N	N	N		NIL	NIL	N	NEG	1	4+	3+	0	2+	0	Y	Y	Y	1	0.8	72.3	1.3	4.8
N	N	N		NIL	NIL		NA	0	2+	2+	0	2+	0	Y	Y	Y		0.9	85.3	1.6	4.1
N	N	N	N	NIL	NIL		POS	0	3+	0	0	2+	0	Y	Y	Y	1	1.1	54.2	2.2	3.9
N	N	N		NIL	NIL		POS	0	3+	0	0	1+	0	Y	N	Y	1	1.1	90.6	1.2	3.1
N	N	N		NA	NA	NA	NA	0	4+	0	2+	3+	0	Y	N	Y	1	5.8	13.8	0.23	3
N	N	N	N	NIL	NIL		NA	2	4+	1+	0	1+	0	Y	N	Y	1	0.8	75.9	2.6	4.6
N	N	N		NIL	NIL		POS	0	2+	0	0	1+	0	Y	N	Y	1	1	84.6	2.4	3.4
N	N	N		NIL	NIL	N	NA	1	4+	2+	0	3+	0	Y	N	Y	2	0.9	83.3	1.5	4
N	N	N		NIL	NIL		NA	0	4+	0	0	3+	0	Y	Y	Y	1	1	62.7	1.1	4.6
N	N	N	NA	NIL	NIL		POS	1	3+	0	0	1+	0	Y	Y	Y	1	1.1	78.2	3.2	3.9
N	N	N	N	NIL	NIL		NA	0	4+	0	0	3+	0	Y	N	Y	1	1	72.6	1.3	4
N	N	N	N	NIL	NIL		POS	0	3+	0	0	0	1+	Y	Y	Y	1	1.4	59.4	3.6	3.2
N	N	N		NIL	NIL		POS	2	2+	0	0	0	0	Y	N	Y	2	1.2	59.5	1.8	3.9
N	N	N	N	NIL	NIL		POS	0	3+	1+	0	3+	0	Y	Y	N	1	1.1	67.8	5.3	4
N	N	N	N	NIL	NIL		POS	0	3+	3+	3+	3+	0	Y	Y	N	1	1.2	56	4.2	3.1
N	N	N	N	NIL	NIL		POS	0	3+	0	0	3+	0	Y	Y	N	1	1.2	55.4	4.8	3.2
N	N	N	NA	NA	NA		NA	1	3+	0	0	3+	0	Y	N	N	1	4.5	66.2	3.4	4
N	N	N		NIL	NIL	N	POS	0	3+	0	0	3+	0	Y	Y	N	1	1.3	74	4.8	3.4
N	N	N		NIL	NIL	N	NA	3	2+	0	0	2+	0	Y	N	N	1	0.8	62	4.3	3
N	N	N	NA	NIL	NIL		POS	1	4+	0	0	3+	0	Y	Y	N	1	1.1	68	4.7	4.1
N	N	N	N	NIL	NIL		NA	0	3+	0	0	3+	0	Y	Y	N	1	1.4	71.7	5.1	3.4
N	N	N		NIL	NIL	N	POS	1	3+	1+	0	1+	0	Y	Y	N	1	0.9	68.9	3.5	3.5
N	N	N	NA	NA	NA		NA	0	4+	0	0	2+	0	Y	Y	N	1	1	60	2.8	3.1
N	N	N	N	NIL	NIL		NA	3	3+	2+	0	2+	0	Y	Y	N	1	7.4	7.9	7.1	3.6
N	N	N	N	NIL	NA		POS	0	3+	0	0	1+	0	Y	Y	N	1	1.2	64	3.7	3.1
N	N	N		NIL	NIL	N	POS	1	4+	2+	0	3+	0	Y	Y	N	1	0.9	98.2	4.5	3.2
N	N	N		NIL	NIL		NA	1	4+	2+	0	3+	0	Y	N	N	?1	0.8	94	5.2	3.1
N	N	N	NA	NIL	NIL		NA	1	2+	0	0	0	1+	Y	N	N	1	0.9	61.1	4.2	3.1
N	N	N		NIL	NIL		POS	0	3+	0	0	2+	0	Y	Y	N	1	0.9	94.7	7.2	3.9
N	N	N		NIL	NIL	N	NEG	0	3+	0	0	0	1+	Y	Y	N	2	0.9	120	3.6	3.4
N	N	N		NIL	NIL		NEG	3	4+	0	0	4+	0	Y	N	N		4.6	20.1	8.2	3.2
N	N	N		NIL	NIL	N	NEG	0	2+	2+	0	0	0	Y	N	N	1	1	96.2	6	4
N	N	N		NIL	NIL		NEG	0	3+	0	0	3+	0	Y	Y	N	2	1.4	35.6	4.6	3.1
N	N	N	N	NIL	NIL		NA	3	2+	0	0	0	1+	Y	N	N	1	3.6	18.3	2.3	3.1
N	N	N		NIL	NIL		NEG	1	4+	2+	0	2+	0	Y	Y	N	1	1.1	89.2	4.6	4
N	N	N		NIL	NIL		NA	0	4+	1+	0	4+	0	Y	Y	N	1	0.9	131.1	4.3	3
N	N	N		NIL	NIL	N	NEG	0	2+	2+	0	0	0	Y	N	N	2	1.2	50.8	4.8	3.1
N	N	N		NIL	N		NEG	0	2+	0	0	0	0	Y	N	N	1	1.1	78.2	4.9	2.9
N	N	N		NIL	NIL	N	POS	0	3+	0	0	1+	0	Y	N	N	1	1	96.2	3.9	3.1
N	N	N	N	NIL	NIL		POS	0	4+	0	0	4+	0	Y	Y	N	1	1.5	36.2	4.4	3.1
N	N	N	N	NIL	NIL		NEG	0	3+	0	0	2+	0	Y	Y	N	1	1.2	72.2	4.5	3.2
N	N	N	NA	NA	NA		NA	3	3+	1+	0	2+	0	Y	N	N	2	4.3	15.1	6.1	3
N	N	N	N	NIL	NIL		NEG	0	3+	0	0	3+	0	Y	N	N	1	1.3	68.2	4.8	3.1
N	N	N		NIL	NIL		NA	0	4+	1+	1+	4+	0	Y	Y	N	1	1.5	52.6	4.5	3.1

N	N	N		NIL	NIL		NA	0	4+	1+	0	1+	0	Y	Y	N	1	1.1	88.2	8.7	3
N	N	N		NIL	NIL	N	POS	1	4+	2+	0	0	0	Y	Y	N	1	1.3	78.7	4.18	3.3
N	N	N		NIL	NIL	NA	NEG	1	N	0	0	0	0	Y	Y	N	2	0.9	112	4.8	3.4
N	N	N		NIL	NIL		NEG	1	N	0	0	0	0	Y	Y	N	2	1	65.3	4.6	3.4
N	N	N		NIL	NIL		NEG	1	2+	1+	3+	1+	0	Y	Y	N		1.2	70.8	4.6	3.9
N	N	N	N	NIL	NIL		NEG	0	2+	1+	0	1+	0	Y	N	N		1	60.7	3.8	3.1
N	N	N		NIL	NIL	N	NEG	0	2+	0	0	1+	0	Y	N	N		1	100.6	3.8	3.8
N	N	N	N	NIL	NIL		NEG	0	2+	0	0	1+	0	Y	Y	N		1	60.8	3.6	3.1

HBSAG	ANTIHCV	HIV	PSA	CT THORA)	OGD	,MMOGRAF	APLA2R	IFTA	IGG	IGM	IGA	C3c	C1Q	ACEI/ARB	M. P	REMISION		CR II	e GFR	uPCR II	ALBUMIN II
N	N	N		NA	NA	NA	NA	0	4+	0	0	4+	0	Y	N	N	1	0.8	NOT DONE	2.7	3.1
N	N	N		NIL	NIL	N	NA	0	4+	4+	1+	2+	2+	Y	N	N	2	1.4	NOT DONE	3.6	3.1
POS	N	N		NIL	NIL		NEG	0	3+	0	0	3+	0	Y	N	N	2	1.9	NOT DONE	6.9	3
N	N	N		NIL	NIL	N	NA	0	3+	0	0	0	0	Y	N	Y PARTIAL		0.8	NOT DONE	3.85	3.1
N	N	N		NIL	NIL	N	NEG	1	4+	2+	2+	4+	3+	Y	N	N	2	1.2	NOT DONE	3.2	3.9
N	N	N	N	NIL	NIL		NEG	1	3+	0	0	3+	3+	Y	N	Y	2	1.1	NOT DONE	2.5	3.9
N	N	N		NIL	NIL		NEG	1	3+	2+	2+	3+	1+	Y	N	Y	2	1.1	NOT DONE	4.3	3.1
N	N	N		NIL	NIL	NIL	NEG	1	3+	1+	3+	0	3+	Y	N	N		0.8	NOT DONE	1.2	3.9
N	N	N		NIL	NIL	N	NA	1	2+	0	0	0	0	Y	N	N	2	1	NOT DONE	3.4	3.7
N	N	N		NIL	NIL	N	NA	0	4+	3+	1+	0	0	Y	N	Y	2	1	NOT DONE	2.8	3.1
N	N	N		NIL	NIL		NEG	1	4+	2+	2+	2+	2+	Y	N	N	2	0.9	NOT DONE	0.9	3.7
N	N	N		NIL	NIL	N	NEG	0	4+	0	0	2+	0	Y	N	Y	2	1.8	NOT DONE	1.2	3.4
N	N	N		NIL	NIL		NA	1	4+	1+	2+	3+	1+	Y	N	N	?1	2.3	NOT DONE	1.8	3.4
N	N	N		NIL	NIL	N	NEG	0	4+	2+	0	4+	0	Y	N	Y	1	1.4	NOT DONE	2.5	3.4
N	N	N		NIL	NIL	N	NEG	1	4+	2+	0	4+	0	Y	N	Y	1	1.2	NOT DONE	4.8	3.1
N	N	N		NIL	NIL		NA	1	4+	3+	2+	3+	2+	Y	N	N	2	0.9	NOT DONE	5.2	4.1
N	N	N	N	NIL	NIL		NA	1	4+	2+	2+	3+	0	Y	N	Y	1	5.8	NOT DONE	4.9	3.1
N	N	N	0.35 ng/ml	NIL	TRAL NODULE		NEG	0	3+	0	0	0	3+	Y	N	N	2	0.9	NOT DONE	3.8	4
N	N	N	NA	NIL	NIL		NEG	0	2+	0	0	0	0	Y	N	Y PARTIAL	2	0.8	NOT DONE	3.17	4.6
N	N	N		NIL	N		NA	2	4+	3+	0	4+	2+	Y	N	Y	2	0.9	NOT DONE	5.6	3.5
N	N	N		NIL	NA		NA	3	3+	0	3+	3+	3+	Y	N	N	2	2.6	NOT DONE	3.5	3.1
N	N	N		NIL	NIL	N	NEG	1	2+	0	0	0	0	Y	N	N	2	0.6	NOT DONE	2.9	3.9
N	N	N		NIL	NIL	N	NA	0	2+	2+	1+	2+	0	Y	N	Y	2	4.6	NOT DONE	5.2	3.1
N	N	N		NIL	NIL		NA	0	4+	2+	3+	3+	3+	Y	N	Y	2	0.8	NOT DONE	0.5	4
N	N	N		NIL	NIL		NEG	0	3+	0	1+	2+	1+	Y	N	Y PARTIAL	2	1.8	NOT DONE	2.66	2.9
N	N	N		NIL	NIL	NIL	NEG	1	4+	1+	3+	4+	3+	Y	N	N	2	0.8	NOT DONE	2.1	4.5
N	N	N		NIL	NIL		NA	0	3+	2+	0	3+	2+	Y	N	N	1	0.9	NOT DONE	3.6	3.6
POS	N	N		NIL	NIL	N	NA	2	2+	0	0	2+	0	Y	N	N	2	0.8	NOT DONE	4.5	4.1
N	N	N		NIL	NIL	N	NA	1	4+	4+	2+	2+	2+	Y	N	Y	2	9.6	NOT DONE	9	4.1
N	N	N		NIL	TRAL NODULE		NEG	1	2+	0	0	2+	0	Y	N	N	2	0.9	NOT DONE	4.1	4.1
N	N	N		NIL	NIL	N	NEG	3	3+	0	0	3+	0	Y	N	Y PARTIAL	2	0.8	NOT DONE	0.33	3.5
N	N	N		NIL	NIL		NA	1	3+	0	2+	3+	2+	Y	N	N	2	1.3	NOT DONE	3.5	4.2
N	N	N	N	NIL	NIL		NA	0	2+	1+	1+	2+	1+	Y	N	N	2	1.4	NOT DONE	5.2	3.2
N	N	N		NIL	NIL		NA	0	4+	3+	0	2+	2+	Y	N	N	2	1	NOT DONE	3.4	3.3
N	N	N	N	NIL	NIL		NA	3	4+	2+	2+	4+	3+	Y	N	N	2	1.6	NOT DONE	3.7	3.2
N	N	N		NIL	NIL	NA	NEG	1	2+	0	0	2+	2+	Y	N	Y	2	0.9	NOT DONE	5.1	3.1
N	N	N		NIL	NIL	N	NA	0	4+	3+	2+	2+	0	Y	N	N	2	0.9	NOT DONE	0.4	3

சுய ஒப்புதல் படிவம்

ஆய்வு செய்யப்படும் தலைப்பு : **மெம்ரேனஸ் நெப்ரோபதி என்னும் சிறுநீரக நோயின் தன்மை பற்றிய ஆய்வு.**

ஆராய்ச்சி நிலையம் : சிறுநீரகத் துறை,
இராஜீவ் காந்தி அரசு பொது மருத்துவமனை மற்றும்
சென்னை மருத்துவக் கல்லூரி,
சென்னை - 600 003.

பங்கு பெறுபவரின் பெயர் : உறவுமுறை :
பங்கு பெறுபவரின் எண். :

பங்கு பெறுபவர் இதனை (✓) குறிக்கவும்

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

நான் இவ்ஆய்வில் தன்னிச்சையாகத்தான் பங்கேற்கிறேன். எந்தக் காரணத்தினாலோ எந்தக் கட்டத்திலும் எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்ஆய்வில் இருந்து விலகிக் கொள்ளலாம் என்றும் அறிந்து கொண்டேன். ☐

இந்த ஆய்வு சம்மந்தமாகவோ, இதை சார்ந்த மேலும் ஆய்வு மேற்கொள்ளும்போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளைப் 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 பயன்படுத்திக் கொள்ளவும் அதைப் பிரசுரிக்கவும் என் முழு மனதுடன் சம்மதிக்கிறேன். ☐

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக்கொள்கிறேன். எனக்குக் கொடுக்கப்பட்ட அறிவுரைகளின்படி நடந்து கொள்வதுடன், இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்றும் உறுதியளிக்கிறேன். என் உடல் நலம் பாதிக்கப்பட்டாலோ அல்லாத எதிர்பாராத வழக்கத்திற்கு நோய்க்குறி தென்பட்டாலோ உடனே அதை மருத்துவ அணியிடம் தெரிவிப்பேன் என உறுதி அளிக்கிறேன். ☐

இந்த ஆய்வில் எனக்கு இரத்தம், சிறுநீர் மற்றும் முழு உடல் பரிசோதனை செய்து கொள்ள நான் முழு மனதுடன் சம்மதிக்கிறேன். ☐

பங்கேற்பவரின் கையொப்பம்..... இடம்..... தேதி
கட்டைவிரல் ரேகை

பங்கேற்பவரின் பெயர் மற்றும் விலாசம்.....

ஆய்வாளரின் கையொப்பம்..... இடம்..... தேதி

ஆய்வாளரின் பெயர்.....

ஆராய்ச்சி தகவல் தாள்

இராஜீவ் காந்தி அரசு பொது மருத்துவமனை சிறுநீரக பிரிவில் வரும் நோயாளிகளில் மெம்ரேனஸ் நெப்ரோபதி என்னும் சிறுநீரக நோயை கண்டறிந்து அதன் தன்மையை ஆராய்வதே இந்த ஆய்வின் நோக்கமாகும்.

இந்த ஆராய்ச்சியின் முடிவுகளை அல்லது கருத்துக்களை வெளியிடும் போதோ அல்லது ஆராய்ச்சியின் போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிட மாட்டோம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

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

இந்த சிறப்புப் பரிசோதனைகளின் முடிவுகளை ஆராய்ச்சியின் போது அல்லது ஆராய்ச்சியின் முடிவின் போது தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

தேதி: