

Original Article

Clinico-Pathological Study of Adult Nephrotic Syndrome at A Tertiary Care Centre of North India in Jammu and Kashmir

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ABSTRACT

Background: Nephrotic syndrome is a potentially life-threatening condition and persistence of nephrotic syndrome portends a poor prognosis with a high risk of progression to end-stage renal disease. The spectrum of diseases leading to Nephrotic syndrome is changing globally. The aim of our prospective study was to analyze the spectrum of adult nephrotic syndrome at a tertiary care centre of North India. **Methods:** Patients in the age group 18-75 years with nephrotic syndrome were consecutively included in the study. Renal biopsies were performed in all patients and were subjected to light microscopy and immunofluorescence (IF). **Results:** A total of 40 adult patients with nephrotic syndrome were enrolled in our study which included 62.5% males and 37.5% females. The mean age of our study population was 34.5(±12.24) with a range of 18-75 years. The most common clinical presentation of our study population was facial puffiness which was present in 100% patients followed by pedal edema in 92.5% and anasarca in 50% of patients. Systemic hypertension was found in 32.5% of the study population. Twenty four hour urine protein excretion ranged from 3.52 g to 14.9 g/ day. Proteinuria was severe with histopathological subtype, minimal change disease (mean >9 g/day). Acute kidney injury was present in 32.5% of the study patients. Hematuria was found in 25% of patients in our study population. Nephrotic syndrome was primary in 87.5% of cases and secondary in rest 12.5%. The commonest histopathological diagnosis in our study population was FSGS constituting 32.5% of the patients. Among secondary glomerular diseases lupus nephritis (LN) and diffuse nephritis (DN) were equally common each representing 5% of the study population. **Conclusion:** There is a considerable heterogeneity in the histologic spectrum of the nephrotic syndrome. However, recent data from west as well as from recent Indian studies depicted changing trend, with FSGS as the leading cause of nephrotic syndrome. FSGS was also the most common biopsy diagnosis in our study population. A large corroborative study needs to be undertaken to substantiate our study results.

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INTRODUCTION:

Nephrotic syndrome (NS) is a perplexing relatively rare clinical entity characterized by heavy proteinuria, hypoalbuminemia, edema and hypercholesterolemia. It is a potentially life-threatening condition and persistence of nephrotic syndrome portends a poor prognosis with a high risk of progression to end-stage renal disease. It also

leads to high risk of cardiovascular complications due to severe hyperlipidemia ^{1,2}. Nephrotic syndrome is divided into primary and secondary types. Focal segmental glomerulosclerosis (FSGS) and Membranous nephropathy (MN) each account for 30% cases of adult Nephrotic syndrome worldwide. A wide range of diseases and drugs can cause nephrotic syndrome. The common ones like

Diabetes Mellitus (DM), Lupus-Nephritis and Amyloid Nephropathy (AN) account for the majority of the cases among various other secondary causes of Adult Nephrotic syndrome ^{2,3}. Focal segmental glomerulosclerosis (FSGS) has emerged as the commonest cause of adult NS in the recently published data from around the world.^{4,5} But, there are regional variations, with minimal change disease (MCD) being the commonest cause of adult NS and FSGS being much less common in studies from Korea and Denmark ^{6,7}. On the other hand, the Italian, Spanish, and Japanese registries report membranous nephropathy (MN) as the most common etiology for adult NS⁸⁻¹⁰. There could be many factors for this variation, and race could be one of them as is evident from the overwhelming evidence of increasing trend of FSGS in adults¹¹.

MATERIALS & METHODS:

The present hospital based observational study was conducted in the Department of Medicine and Department of Nephrology Government Medical College and associated super-specialty Hospital, Srinagar over a period of one and a half years after obtaining the ethical clearance from the Institutional Ethical Committee. A total of 40 patients were enrolled for the study. Inclusion Criteria: All nephrotic syndrome patients aged ≥ 18 years of age. Exclusion Criteria: Patients aged < 18 years and patients having any contraindication for biopsy. Nephrotic syndrome was defined by heavy proteinuria (>3.5 g/day), Hypoalbuminemia (<3.5 mg/dl), edema and hyperlipidemia¹. Acute kidney injury (AKI) was defined on the basis of KIDGO guidelines and absolute serum creatinine of 1.5 or greater was also categorized as acute kidney injury ¹². All patients enrolled in the study underwent thorough history taking and meticulous

physical examination including general physical and systemic examination. Laboratory investigations like Complete blood count(CBC), Kidney function test (KFT), Blood sugar, liver function test(LFT), Coagulation profile, lipid profile, detailed routine urine examination, 24 hour urinary protein, triple serology (hepatitis B surface antigen, anti-hepatitis C antibody, Anti-HIV antibody), Anti-nuclear antibody (ANA), and complement assays were sent in all the patients. Additional investigations such as anti-double stranded deoxyribonucleic acid antibody (anti-ds DNA) and other relevant investigations were performed in selected cases wherever indicated. All patients underwent an ultrasound evaluation of the kidneys followed by renal biopsy. The biopsy was performed under ultrasound guidance and local anaesthesia using Bard Trucut biopsy gun. Patients were observed for 24 hours for procedure related complications. The biopsy material was subjected to histopathology examination (HPE) with Light microscopy (LM) and immunofluorescence (IF). All the slides for histopathological examination (HP) were studied after staining with Haematoxylin and Eosin (H&E) and periodic acid Schiff stains, Jones silver and Masson's trichome. Congo red staining was performed in selected cases.

Statistical analysis: Data was entered into a Microsoft Excel spreadsheet. Continuous variables were summarized as mean and standard deviation. To summarize categorical variables, frequencies and percentages were reported. The relationship between two categorical variables was analysed using Pearson Chi-square test. A p-value of ≤ 0.05 was considered as statistically significant. Statistical hypothesis tests were carried out using www.openepi.com.

RESULTS:

In our study 40 patients were enrolled, among which 62.5% (n=25) were males and 37.5% (n=15) were females with a male to female ratio of 1.66:1. Mean age in our study group was 34.5 ± 12.24 with a range of 18 to 75 years. Figure 1 shows the age group wise distribution of patients. About 82.5% (n=33) of the total patients were less than 40 years while as only 17.5% of patients were above 40 years

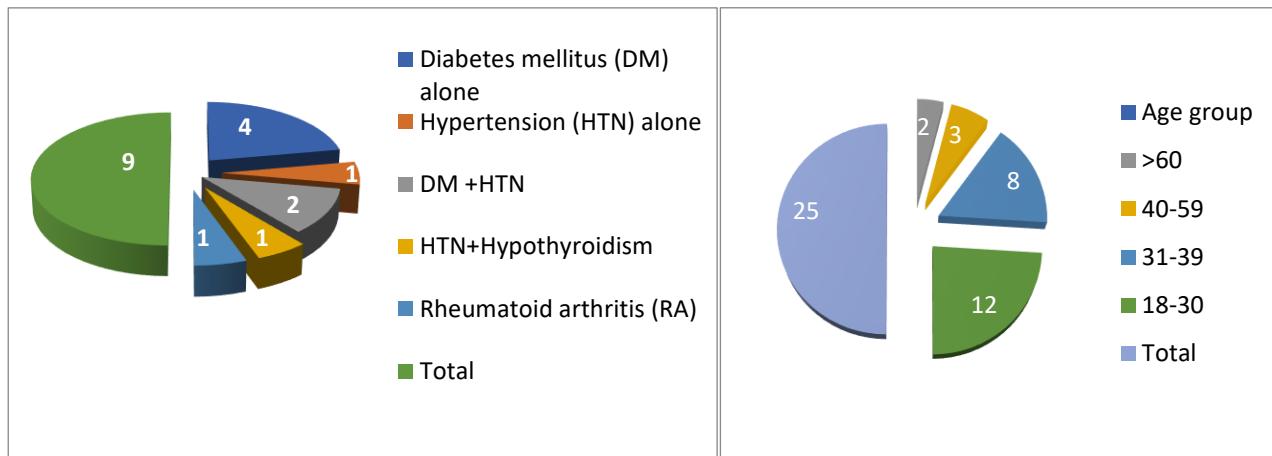


Figure 1 Distribution of age groups

In our study 22.5% (n=9) had comorbidities among which diabetes mellitus (DM) was the most frequent comorbidity. DM was found in 15% (n=6) of patients either alone 10% (n=4) or in combination with hypertension (HTN) as seen in 5% (n=2) of patients. A total of 10% (n=4) of patients were already on antihypertensive medications. As shown in figure 3, the

Figure 2 Comorbidities in study population

most frequent symptoms reported by nephrotic syndrome patients on presentation was facial puffiness and pedal edema present in 100% (n=40) and 92.5% (n=37) of patients respectively. Other common symptoms reported were abdominal distension and anasarca in 50% (n=20) of the patients each. Scrotal edema among males was present in 30% (n=12) and Vulval edema among females was found in 20% (n=8) of patients in study population. Oliguria was seen in 25% (n=10) and decreased appetite in 10% (n=4) of patients besides other less common symptoms as mentioned in the figure 2. The mean duration of symptoms prior presentation to hospital was 6 weeks with a range of 1 week to 22 weeks.

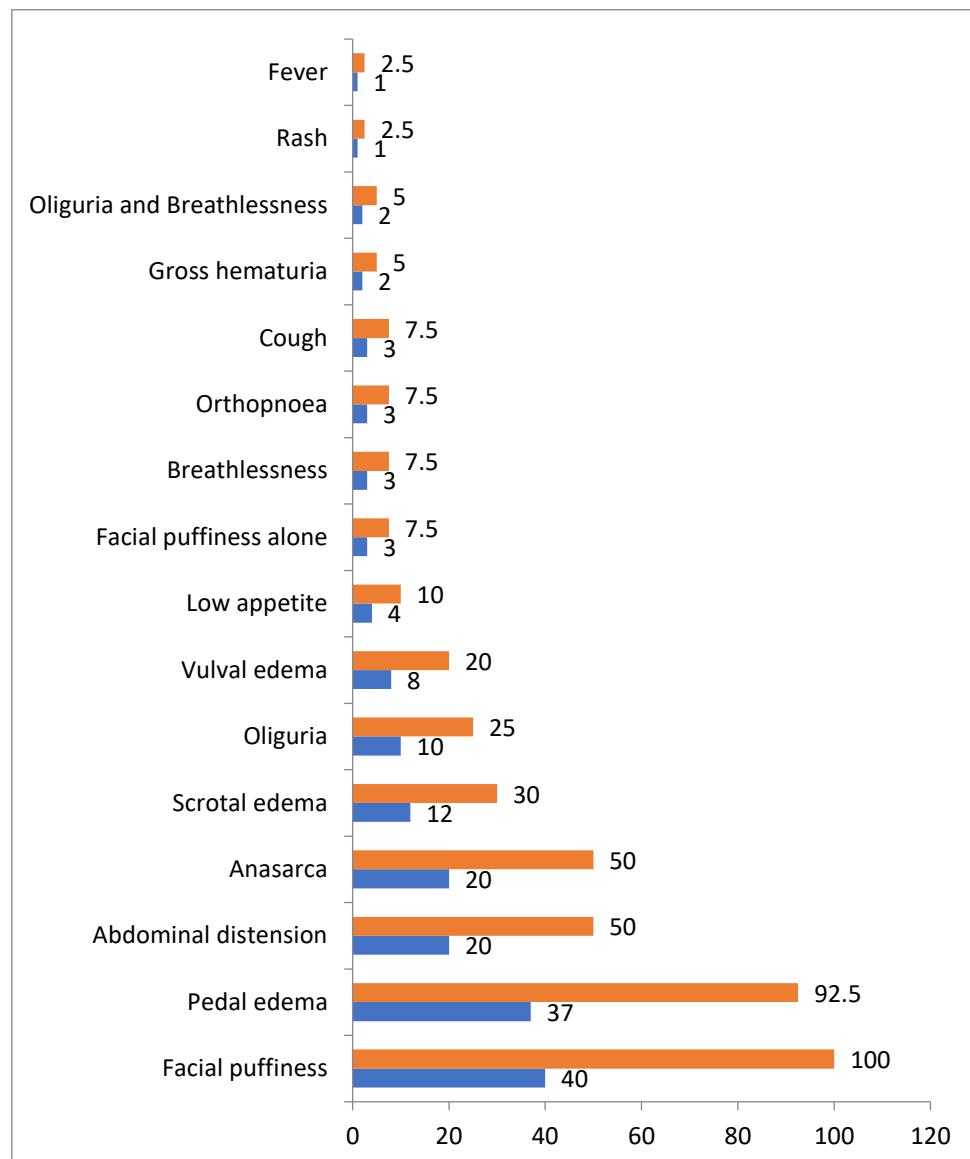


Figure 3 Presenting symptoms of nephritic syndrome in study population

We found hematuria (including 2 patients with gross hematuria) in 25% (n=10) of the study population which included males 20% (n=8) and females 5% (n=2). This higher incidence of hematuria in males was found to be statistically significant with a **p value of 0.008**. About 67.5% (n=27) of adult nephrotic syndrome patients had normal renal function. Acute kidney injury was found in 32.5% (n=13) of patients. Among males 36% (n=9) had acute kidney injury and 26.7% (n=4) of females were found to have acute kidney injury. The mean serum cholesterol in our study was 288.5(±62.5) with a range of 189-501 mg/dl. In our study 37.5% (n=15) of patients had 24 hr urinary protein between 3.5 to 6 grams. The 24 hr urinary protein excretion was in the range of 6.1 to 9.0 grams in 32.5% (n=13) of patients while as 24 hr urinary protein excretion in the range of 9.1 to 12 gram and 12.1-15 grams had representation of 15% (n=6) each.(Table 1)

Table 1 Biochemical parameters in study subjects

Biochemical Parameter	Male %	(n)	Female %	(n)	Total %	(n)	P value
Hematuria							
Hematuria present	8	20	2	5	10	25	0.008

No Hematuria	17	42.5	13	32.5	30	75	
Kidney function							
Normal kidney function	11	27.5	16	40	27	67.5	0.52
Acute kidney injury	4	10	9	22.5	13	32.5	
Serum cholesterol mg/dl							
<200	1	2.5	2	5	3	7.50	0.214
200-249	4	10	7	17.5	11	27.50	
250-300	5	12.5	14	35	19	47.50	
>300	5	12.5	2	5	7	17.50	
24 Hour Urinary Protein Excretion In Grams/Day							
3.5-6 grams	6	15	9	22.5	15	37.5	0.987
6.1-9 grams	5	12.5	8	20	13	32.5	
9.1-12 grams	2	7.5	4	10	6	15	
12.1-15 grams	2	7.5	4	10	6	15	

The mean serum albumin in our study was 2.57(+0.65) with a range of 1 to 3.3 g/dl. The serum albumin was less than 2.5 g/dl in 22.5% (n=9) of patients and greater than 2.5g/dl in 77.5% (n=31) patients. Hypocomplementemia was found in 7.5% of the study population. The ANA was positive in 7.5% of patients. In our study 87.5% (n=35) of patients had primary Glomerular disease with males 55% (n=22) and females 32.5% (n=13) as shown in table 2

Table 2 Distribution of glomerular diseases in study subjects

	Primary glomerular disease		Secondary glomerular disease		Total (%)
	Frequency	Percentage	Frequency	Percentage	
Males	22	55	3	7.5	25(62.5)
Females	13	32.5	2	5	15(37.5)
Total	35	87.5	5	12.5	40(100)

As shown in table 3, FSGS was found to the most frequent histological lesion accounting for 32.5% (n=13) of patients with males 22.5% (n=9) and females 10% (n=4) of the total (n=40). FSGS was followed by MN in 22.5% of the patients with males 17.5% (n=7) and females 5% (n=2). The third frequent histopathological diagnosis found was MCD accounting for 17.5% of the study patients with 10% (n=4) females and 7.5% males (n=3)

Table 3 Gender wise distribution of Histopathology

	Male(n=25)		Female(n=15)		Total		P Value
	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	
Biopsy							
FSGS	9	22.5	4	10	13	32.5	0.541
MN	7	17.5	2	5	9	22.5	0.283
MCD	3	7.5	4	10	7	17.5	0.237
IgAN	2	5	1	2.5	3	7.5	0.876
DPGN	0	0	1	2.5	1	2.5	0.191
MPGN	1	2.5	1	2.5	2	5	0.707
DN	1	2.5	1	2.5	2	5	0.707
LN	1	2.5	1	2.5	2	5	0.707
AN	1	2.5	0	0	1	2.5	0.191
Total	25	62.5	15	37.5	40	100	

The most common histopathological diagnosis in patients above 40 years of age was Membranous nephropathy (MN) accounting for 12.5% (n=5) of the total cases. MN had representation of just 10% (n=4) of the total cases in age group less than 40. All MCD patients were below 40 years of age and frequency of MCD in this age group accounted for 17.5% (n=7) of the total patients, however it was statistically insignificant with a **p value of 0.17**. FSGS was the most common cause in patients of age group less than 40 years and next most common in patients above 40 years of age. The higher incidence of MN above 40 years of age was found statistically significant with a **p value of 0.015** as shown in Table 4.

Table 4 Age wise Histopathology distribution

Histopathology	Age group				Total n (%)
	<40 years		>40 years		
	Frequency	Percentage	Frequency	Percentage	
AN	1	2.5	0	0	1 (2.5%)
DN	1	2.5	1	2.5	2 (5%)

DPGN	1	2.5	0	0	1 (2.5%)
FSGS	11	27.5	2	5	13 (32.5%)
IgAN	3	7.5	0	0	3 (7.5%)
LN	2	5	0	0	2 (5%)
MCD	7	17.5	0	0	7 (17.5%)
MN	5	12.5	4	10	9 (22.5%)
MPGN	2	5	0	0	2 (5%)
TOTAL	33	82.5	7	17.5	40 (100%)
P Value=0.307					

In our study 32.5% of patients had acute kidney injury. Among patients with diabetic nephropathy 50% had AKI. All (100%) LN patients had AKI which was statistically significant with a P value of 0.03. None of the patients among MCD had renal dysfunction which was statistically significant with 0.04 as P value. About 38.46% of FSGS patients were found to have AKI as shown in table 5. Out of total 6 diabetic patients in our study only 33.33% (n=2) had diabetic nephropathy. Rest 66.67% (n=4) had non-diabetic nephropathy with 33.33% (n=2) MN and 33.33% (n=2) FSGS.

Table 5 Histopathology wise acute kidney injury

Biopsy	Frequency	Percentage	P Value
AN	0	0	0.37
DN	1	50	0.58
DPGN	0	0	0.5
FSGS	5	38.46	0.57
IgAN	0	0	0.21
LN	2	100	0.03
MCD	0	0	0.04
MN	4	44.44	0.54
MPGN	1	50	0.58
Total	13		

DISCUSSION:

In our study, clinical characteristics and renal biopsy findings of 40 adult nephrotic syndrome patients were analysed. Males constituted 62.5% (n=25) and females 37.5% (n=15) of study population with a male to female ratio of 1.66:1. A R Reshi et al., (2008)¹³ in a study conducted at tertiary care hospital Kashmir also revealed male preponderance (60.2%). In a study conducted by Golay V et al., (2013)¹⁴ males constituted 57.8% of the study population. Similarly a study conducted in a north-Indian tertiary care hospital by M Rathi et al., (2014)¹⁵ also showed male preponderance in the occurrence of nephrotic syndrome in adults (60.2%). Likewise a study conducted in eastern state of India by Pradeep Chakraborty et al., (2021)¹⁶ also showed a slight male preponderance (54%). Mean age of our study patients was 34.5 ± 12.24 with a range of 18-75 years. The mean age of study group of Golay V et al., (2013)¹⁴, M Rathi et al., (2014)¹⁵, Amit V et al., (2015)¹⁷ and Pradeep Chakraborty et al., (2021)¹⁶ were 33.68, 31.5, 36.5 and 34.56 years respectively which was concordant with our study population. The mean duration of symptoms of our study patients before presenting to our hospital was (6 ± 3.5 weeks) with a range of 1 week to 22 weeks. About 67.5% of patients presented to hospital within 12 weeks which is concordant with the observation reported by A R Reshi et al., (2008)¹³ in their study where 69% of patients presented within 4 months after first appearance of symptoms. Nevertheless, there is a sparse data viz a viz symptom duration in various studies of adult nephrotic syndrome. The most common symptom in our patients was edema. Facial puffiness was present in

100% patients of our study group while 92.5% had pedal edema. A R Reshi et al., (2008)¹³ reported facial puffiness and pedal edema in 99% and 91% of patients respectively. Similarly, M Rathi et al., (2014)¹⁵ found edema in 100% of patients. Similarly, Khirsagar M et al., (2017)¹⁸ in Mumbai reported facial puffiness as the predominant finding present in 100% of study patients. Oliguria was found in 30% of our patients which was concordant with study observations of Khirsagar M et al., (2017)¹⁸ who reported oliguria in 36% of patients. However, in studies conducted by Reshi et al., (2008)¹³ and M Rathi et al., (2014)¹⁵ oliguria was found in 42.7% and 10.4% respectively. Hypertension was found in 32.5% of our patients which was concordant with the observations of study conducted by Golay V et al., (2013)¹⁴ who reported hypertension in 34.94% patients. Similarly Faye M et al., (2016)¹⁹ reported hypertension in 40% of his adult nephrotic cohort. Anirban Sarkar et al., (2018)²⁰ from Eastern India reported hypertension in 36% of adult nephrotic syndrome patients in his study. Hematuria was found in 25% of our patients which was concordant with the studies conducted by Golay V et al., (2013)¹⁴ and Anirban Sarkar et al., (2018)²⁰ who reported hematuria in 28.5% and 35% respectively. In our study hematuria was more common in males than females which we found statistically significant (P value ≤ 0.05). It has been reported that males irrespective of age have higher incidence of glomerular hematuria than females²¹. Mean 24 hour urinary protein excretion in our study group was $6.93 (\pm 3.172)$ with a range of 3.52-14.9. Study conducted by Golay V et al., (2013)¹⁴ reported the mean 24 hour urinary protein excretion of 6.31 ± 3.68 . Similarly

Faye M et al., (2016)¹⁹ reported mean proteinuria of 6.8 ± 4.8 grams per day on the other hand M Rathi et al., (2014)¹⁵ reported mean proteinuria of 4.91 ± 1.98 grams per day in their study. The mean serum Cholesterol in our study group was 288.5 ± 62.5 mg/dl with a range of 189-501 which was concordant with study conducted by M Rathi et al., (2014)¹⁵ who reported mean Cholesterol of 325 ± 109.9 mg/dl. Mean serum Albumin in our study was 2.57 ± 0.65 mg/dl which was concordant with the study results of M Rathi et al., (2014)¹⁵ and Golay V et al., (2013)¹⁴ who found it to be 2.6 ± 0.53 mg/dl and 2.12 ± 0.71 mg/dl respectively. Studies have shown that the incidence of Acute kidney injury in adults with primary nephrotic syndrome varies considerably and can be up to 44.9% (Honghua Lu et al., 2022)¹² In our study acute kidney injury (AKI) was found in 32.5% of the patients. Moreover we observed that 38.4% of biopsy proven FSGS patients had AKI. Anirban sarkar et al., (2018)²⁰ had AKI in 22% of the patients Reshi et al., (2008)¹³ found higher incidence of AKI in FSGS patients (22%). We found Hypocomplementemia and ANA positivity in 7.5% of patients each which is in accordance with the observations made by Anirban sarkar et al.,(2018)²⁰ who in their study conducted in eastern India reported Hypocomplementemia in 10% of study patients. Although there is a limited data regarding the spectrum of Adult Nephrotic syndrome, however a significant histopathological heterogeneity could be traced from the literature. In our study we found that primary glomerular diseases accounted 87.5% of cases while 12.5% were diagnosed with secondary glomerular diseases. This observation was concordant with studies worldwide. Most of the studies from India show predominance of primary glomerular diseases as cause of nephrotic syndrome as reported by A R Reshi et al., (2008)¹³, Golay V et al., (2013)¹⁴, M Rathi et al.,(2014)¹⁵, Amit V et al., (2015)¹⁷, Khirsagar M et al., (2017)¹⁸, Pradeep Chakraborty et al., (2021)¹⁶ where primary glomerular diseases accounted for 91.73%, 88.05%, 89%, 80.9%, 78.3%, 88% respectively. Perkowska-Ptasinska A (2017)²² from polish registries reported primary glomerular diseases accounting for majority of the cases of adult Nephrotic syndrome (67.6%). Our study depicted that FSGS is the most common cause of idiopathic nephrotic syndrome accounting for 32.7% of study patients. Faye M et al.,(2016)¹⁹ from African country also found FSGS as the commonest cause of adult nephrotic syndrome with representation of 54%. Nevertheless this percentage is higher than our study and could be partly explained by significant racial differences. Asian studies also report diverse and changing spectrum of nephrotic syndrome Balakrishnan et al., (2008)²³ in a study conducted at CMC Vellore reported changing trend with increasing frequency of FSGS and found FSGS as the predominant cause of adult nephrotic syndrome (16.8%) followed by MCD and MN. Grace M Thomas et al., (2012)²⁴ from Kerala also reported FSGS as the commonest histopathological diagnosis among patients with adult nephrotic syndrome. Similarly Golay V et al., (2013)¹⁴ in his study at Kolkata reported that FSGS is the most common cause of adult nephrotic syndrome accounting for 27.4% of cases followed by MCD (27.1%) and MN (24.6%). A North Indian study by M

Rathi et al.,(2014)¹⁵ reported five fold increase in the incidence of FSGS (6.5% vs 30.6%) at a tertiary care hospital as a cause for adult nephrotic syndrome and concluded that FSGS is the most common cause of adult nephrotic syndrome in North India. A recent study conducted by Pradeep chakraborty et al., (2021)¹⁶ at Kolkata found FSGS as the most predominant cause of adult nephrotic syndrome accounting for 54% of cases which was higher than our study. This significant difference can partly be explained the use of electron microscopy in their study group. Some studies were discordant with our study results. Khirsagar M et al., (2017)¹⁸ reported MCD as the most common cause of adult nephrotic syndrome accounting for 26.38% of cases followed by MPGN (16.17%) which was discordant with our study. In a Kashmir based study conducted by AR Reshi et al.,(2008)¹³ MCD was found as the most common cause of adult nephrotic syndrome accounting for 33.52% followed by FSGS(19.07%). The relatively higher frequency of FSGS in our study within the same milieu of Kashmiri population may reflect a real increase in this entity in the same manner as reported by other studies in their respective centres^{11,13,25} or partly by improved renal biopsy techniques. In our study MN was the second most common cause of idiopathic nephrotic syndrome accounting for 22.5% of the cases. Grace M et al.,(2012)²⁴ and M Rathi et al.,(2014)¹⁵ reported 32% and 24.4% MN incidence respectively. In a study conducted by Golay V et (2013)¹⁴ the frequency of MN (22.44%) was also similar to our study, however there was a slight predominance of MCD over MN (23.9% vs 22.44%). Although FSGS was overall the most common cause in our study group, however we found MN as the predominant cause of idiopathic nephrotic syndrome followed by FSGS in older age group (>40 years). MN accounted for 42.8% of study patients above 40 years age which was statistically significant (p value of 0.005). This finding was consistent with study results of M Rathi et al., (2014)¹⁵ which reported that MN accounted for 32.5% cases of NS in age group of >40 years. Similarly John J Sim et al., (2016) ²⁵ also reported MN to be the second most common cause of older age group nephrotic syndrome with FSGS being the leading cause in their study. MCD was the 3rd most common cause of idiopathic nephrotic syndrome which was seen in 17.5% of our study patients. Anirban sarkar et al., (2018)²⁰ reported MCD as the third most common cause and was found 19% of the patients which was in line with our study result. John J Sim et al.,(2016)²⁵ in their study found MCD as the 3rd leading cause of adult nephrotic syndrome. IgA nephropathy (IgAN) accounted for 7.5% and MPGN for 5% of the cases which was in line with the study result of Golay V et al.,(2013)¹⁴. The most common secondary glomerular diseases as a cause for nephrotic syndrome were diabetic Nephropathy and Lupus Nephritis accounting each for 5% of the cases. Pradeep Chakraborty et al, (2021)¹⁶ and Golay v et al(2013)¹⁴ found Lupus Nephritis as the most common cause of nephrotic syndrome accounting for 4% and 6.58% of the study population respectively. Khirsagar M et al., (2017)¹⁸ found DN in 4.25% of patients although most common SGD was Amyloidosis seen in 7.23% of patients. We found non-diabetic

nephropathy as a cause of adult nephrotic syndrome in 66.6% of diabetic patients. The prevalence of non-diabetic renal disease (NDRD) in diabetic patients has been reported to range from 27 to 79% (Lee E.Y et al).²⁶

Limitations of our study : Our study had few limitations. Firstly, it was a single Centre study. Secondly the sample size was small. Thirdly, there was non- availability of electron microscopy at our Centre, the availability of which could have had bearing on our study results.

CONCLUSION:

There is a considerable heterogeneity in the histologic spectrum of the nephrotic syndrome. However, recent data from west as well as from recent Indian studies observed a changing trend, with FSGS as the leading cause of nephrotic syndrome. FSGS was also the most common biopsy diagnosis in our study population. In our study non- diabetic nephropathy was the most common cause of nephrotic syndrome in diabetic patients. A large corroborative study needs to be undertaken to substantiate our study results.

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Conflicts Of Interest: There are no conflicts of interest

Ethics Consideration: The study was conducted after proper permission from the Chairman Ethical Committee Government Medical College Srinagar. A proper informed consent was taken from the participants for renal biopsy and other non-invasive investigations.

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Author Contribution: RKK - concept and design of the study, prepared first draft of the study. MA – interpreted the results and reviewed the literature. MAD - manuscript preparation. PBA - statistically analyzed and interpreted the results. NAP, HMUD, ARA and contributed for review of literature.

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