



# GLOMERULONEPHRITIS; DISTRIBUTION OF BIOPSY PROVEN GLOMERULONEPHRITIS IN KHYBER PAKHTUNKHWA PROVINCE OF PAKISTAN, A SINGLE CENTRE STUDY.

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**ABSTRACT... Background:** The histological pattern and frequency of glomerular diseases differs according to the geographic area, race, age and indications for renal biopsy. This study was conducted to evaluate the frequency of different histological patterns of glomerulonephritis during a 10 years period at our institute. **Study Design:** Retrospective Case series. **Period:** 1<sup>st</sup> January 2007 to 31<sup>st</sup>, December 2017. **Study Setting:** Institute of kidney diseases, Hayatabad Medical Complex Peshawar, Pakistan. **Results and Discussion:** Clinical records of 415 native renal biopsies performed in patients with mean age  $27.17 \pm 14.98$  years were included in this study. Males were 266 (64.1%) and females 149 (35.9%). Data was analysed for three age groups separately, Children (<18 years) 147 (35.5%), Adults (18-59 years) 253 (61.0%) and elderly (>60 years) 15 (3.6%). Primary GN (glomerulonephritis) was the most common (74.21%) followed by secondary GN (26.41%). Among primary glomerular diseases, Focal segmental glomerulonephritis (FSGS) was (29.6%), membranoproliferative glomerulonephritis (MPGN) also known as mesangiocapillary glomerulonephritis constituted 19.5% and Membranous glomerulonephritis (MGN) was the third most common (16.6%). Among secondary GN, acute tubular necrosis (ATN) was the most common (25.4%), followed by amyloidosis (14.7%), hypertensive nephropathy (13.7%) and lupus nephritis (12.8%) respectively. There was a slight male predominance in all types of primary GN except for focal necrotizing GN and most of the secondary types except lupus nephritis and chronic tubulointerstitial nephritis (TIN). Below 18 years, MPGN was (58.3%), focal necrotizing GN (57.1%) and minimal change disease (MCD) was (52.2%). Crescentic GN (89.5%), MGN (74.5%), immunoglobulin A (IgA) nephropathy (72.7%), chronic sclerosing GN (CSGN) (64.7%) and FSGS (56%) were more common in adults. Frequency of immunoglobulin M (IgM) nephropathy (50%) was equal in children and adults. In elderly patients, the commonest GN reported was hypertensive nephropathy (28.6%), amyloidosis (6.7%) and MGN (5.9%). **Conclusion:** Among the wide variety of histological patterns, FSGS was the commonest GN in adults followed by MPGN and MGN. Among adults, primary GN was more common. When compared with other studies, FSGS is more common in the present study and some Indian studies, while membranous GN is more common in other regional countries.

**Key words:** Focal Segmental Glomerulonephritis (FSGN), Glomerulonephritis (GN), Immunoglobulin A, Membranous Glomerulonephritis (MGN), Minimal Change Disease (MCD), Nephropathy (IgA), Nephrotic Syndrome, Renal Biopsy.

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## INTRODUCTION

Glomerulonephropathies are the major contributing morbidity to Chronic kidney diseases (CKD) throughout the world.<sup>1,2</sup> Different types of glomerulonephritis (GN) in different populations vary according to their race, region, gender, age and socioeconomic development.<sup>3</sup> In 1999, 53.0% and in 2004, 47.3% people receiving dialysis had CKD secondary to chronic glomerulonephritis

as stated by Beijing dialysis registry.<sup>3</sup> The exact prevalence and incidence of CKD in Pakistan and India has not been estimated but the available data shows that chronic GN contributes almost one third cases to the overall burden of the problem. This data comes from individual studies as local and national registries for renal biopsies are not maintained in Pakistan.<sup>4</sup>

Apart from primary GN, glomeruli are affected by infections, environmental factors and systemic diseases like diabetes and hypertension.<sup>5</sup> With time, the patterns of glomerular disease is changing in different regions, races, ethnicities as demonstrated by some studies. This suggests the possibility of multifactorial contribution to the glomerulonephritis.<sup>6,7</sup>

Renal biopsy is one of the most important tool in the hand of nephrologists to determine the cause and type of glomerular diseases. Renal biopsies are of utmost importance in the evaluation of patients with proteinuria, haematuria and renal impairment. It helps to establish an accurate diagnosis, decide specific treatment options and predict the prognosis. There is limited data available on the prevalence of different types of glomerulonephritis in Pakistan. Throughout the world immunoglobulin A nephropathy (IgA) has been described as the most prevalent nephropathy as proven by renal biopsy.<sup>8-10</sup>

Recent analysis of renal biopsy specimens from several institutions in the United States revealed that the incidence of focal segmental glomerulosclerosis (FSGS) has increased over the past 20 years. The incidence of FSGS has also increased in Asia, Brazil and India making it the most frequent reported primary GN in some centres.<sup>11,12</sup> In adults FSGS is becoming the leading cause of idiopathic nephrotic syndrome and being increasingly reported in children as well.<sup>13</sup> Membranous glomerulonephritis (MGN) present as nephrotic syndrome and renal insufficiency. Some studies reported higher incidence in male while one study reported the opposite reports.<sup>14-17</sup>

Secondary form of GN are more common in developing and tropical countries owing to high prevalence of certain infections like Malaria, Streptococcus and schistosomiasis.<sup>18</sup> Hypertensive and Diabetic nephropathy are the two secondary leading causes of CKD.<sup>19</sup> To find the situation at our centre we retrospectively analysed renal biopsy findings of past 10 years.

## Method for Renal Biopsy

Patients who were biopsied had one of the following indications. Nephrotic syndrome and acute nephritic syndrome with presence of red blood cell casts on urine microscopy or dysmorphic red cells, temporally associated with acute renal failure with or without new onset hypertension. Acute renal failure with impaired renal functions which had developed in days to weeks. Rapidly progressive renal failure, sub-acute decline in renal function, developing over weeks to months. Renal biopsies were also taken from cases where 24 hour urinary protein was < 3 gm but had associated hematuria or suspected connective tissue disorders like SLE. Renal biopsy was taken in diabetic patients with Nephrotic/ Nephritic presentation without Diabetic retinopathy on ophthalmologist consultation. All biopsies were taken from native kidneys with a core aspirate 18G needle operated via an automated gun. This needle has internal diameter of 300-400 micrometre slightly more than the diameter of adult glomeruli of 200-250 micrometre.

## RESULTS

### Patients Demographic Features

We analysed record of 415 renal biopsies from January 2007 to December 2016. The biopsies were examined by light microscopy and immunofluorescence (IMF) microscopy. Electron microscopy (EM) was not performed in any case due to unavailability. The renal tissue was not adequate for diagnosis in 5 biopsies (1.2%). There were more males (64.1%) than females (35.9%) in the study population. Mean age for all the patients at the time of biopsy was  $27.17 \pm 14.98$  years. 61% of the biopsies came from adults, 35.5% from children and 3.6% from elderly patients as shown in Table-I.

The primary GN (74.21%) were the most frequent findings followed by secondary GN (26.41%). Among primary glomerular diseases, FSGS (29.6%) was reported to be the most common GN. Together MPGN constituted 19.5% of all primary GN. MGN was the third most common GN accounting for 16.6% cases followed by CSGN

(11%) and Crescentic GN (6.2%) respectively. Focal necrotizing GN (2.3%) was found to be the least common among the primary GN following IgM Nephropathy (3.9%) and IgA Nephropathy (3.6%) as shown in Figure-1.

Among secondary GN ATN (25.4%) was the most common GN followed by amyloidosis (14.7%), hypertensive nephropathy (13.7%) and lupus nephritis (12.8%), respectively. Diabetic nephropathy has been reported in only one case 1. Together others types accounted 19.6% of the secondary GN as shown in Figure-2.

There is slight male predominance in all types of primary GN except focal necrotizing GN which is common among females as shown in Figure-3. Similarly, male predominance was observed in all types of secondary GN except chronic TIN and LN where female predominance was common as shown in the Figure-4.

Data when further analysed for different age

groups revealed MPGN (58.3%), focal necrotising GN (57.1%) and MCD (52.2%) as predominant in children. Among adults Crescentic GN (89.5%), membranous GN (74.5%), IgA nephropathy (72.7%), CSGN (64.7%) and FSGS (56%) were more reported in adults. IgM frequency (50%) was equal in children and adults. In elder patients the common GN reported were hypertensive nephropathy (28.6%), amyloidosis (6.7%), Membranous GN (5.9%), MCD (4.3%), MPGN (3.3%) and FSGS (2.2%), respectively as shown in Figure-5.

Patients Demographics	Mean ± SD/ N (%)
Total number of patients	415
Mean Age (years)	27.17 ± 14.98
Males	266 (64.1)
Females	149 (35.9)
Children (<18 years)	147 (35.5%)
Adults (18-59 years)	253 (61.0%)
Elderly (>60 years)	15 (3.6%)

**Table-I. Patient's demographic features  
SD= Standard deviation, N= Number**

Ref.	Present Study.	Mubarak et al. 2011 (29)	Garyal and kaffe 2008 (30)	Zhou et al. 2009 (3)	Rathi et al. 2014 (24)	Nadium et al. 2013 (21)	Huraib et al. 2000 (20)	Ibrahim and Fayed 2012 (31)	Jennifer et al. 2009 (32)	Chang et al. 2009 (33)	Nair and Walker 2006 (34)
<b>Duration</b>	2006-2016	1996-2006	2001-2007	1997-2011	2002-2007	210-2011		2003-2008	1976-2005	1987-2006	
<b>Place</b>	Pakistan/ IKD, Peshawar	Pakistan/ SIUT Karachi	Nepal	China	India	Sudan	Saudi Arabia	Egypt	Brazil	Korea	USA
<b>Number</b>	415	316	137	1374	364	83	782	924	1844	1818	4504
<b>Glomerulonephritis (%)</b>											
<b>FSGS</b>	21.9	39.87	8	6	36.6	29.6	21.3	20.02	5.7	5.6	12.8
<b>Mem GN</b>	12.3	26.58	42.3	29.5	24.4	11.2	10.6	7.03	29.4	12.3	8.4
<b>MPGN</b>	14.5	8.41	21.9	1.5	17.9	26.8	20.7	10.49	9.6	4	
<b>MCD</b>	5.5	14.82	10.2	25.3	14.8	16.9	11.6	8.55	9.8	15.5	1.4
<b>IgA ephropathy</b>	2.7	2.53	2.9	20	1.8	5.6	6.5	-	38.3	28.3	3.4
<b>IgM ephropathy</b>	2.9	-	-	-	-	-	-	-	-	-	10.3
<b>CSGN</b>	8.2	-	2.2	0.7	2.8	-	20.7	13.96	-	-	-
<b>Crescentic GN</b>	4.2	-	-	-	-	-	8.8	-	-	-	-
<b>Focal Necrotizing GN</b>	1.7	-	-	-	-	-	4.3	3.68	-	-	-

**Table-II. A comparative reference of related studies**

GN= Glomerulonephritis, FSGS= Focal segmental glomerulosclerosis, Mem= Membranous, MPGN= Membranoproliferative glomerulonephritis, MC= Mesangiocapillary, MCD= Minimal change disease, IgA= Immunoglobulin A, IgM= Immunoglobulin M, CS= Chronic sclerosing.

Distribution of Primary Glomerular Diseases

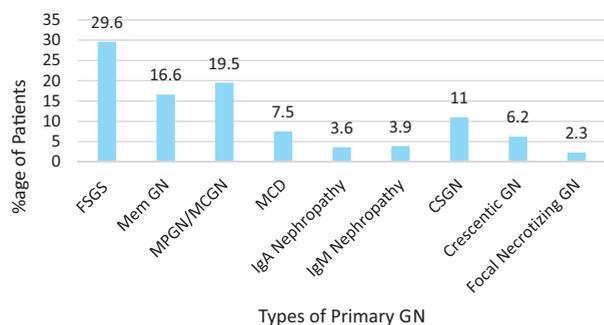


Figure-1. Distribution of primary glomerular diseases and their percentages

GN= Glomerulonephritis, FSGS= Focal segmental glomerulosclerosis, Mem= Membranous, MPGN= Membranoproliferative glomerulonephritis, MC= Mesangiocapillary, MCD= Minimal change disease, IgA= Immunoglobulin A, IgM= Immunoglobulin M, CS= Chronic sclerosing,

gender specific distribution of secondary glomerular diseases

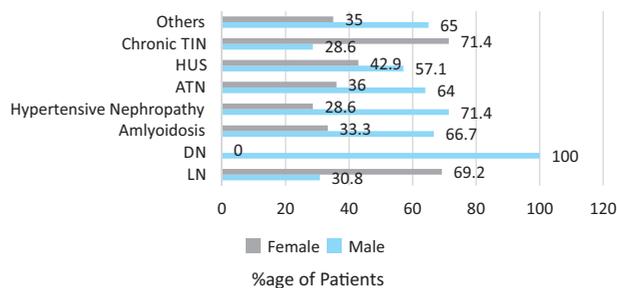


Figure-4. Gender distribution of secondary glomerular diseases

LN= Lupus nephritis, DN= Diabetic nephropathy, ATN= Acute tubular necrosis, HUS=Haemolytic uremic syndrome, TIN= Tubulointerstitial nephritis

Pattern of Secondary GN

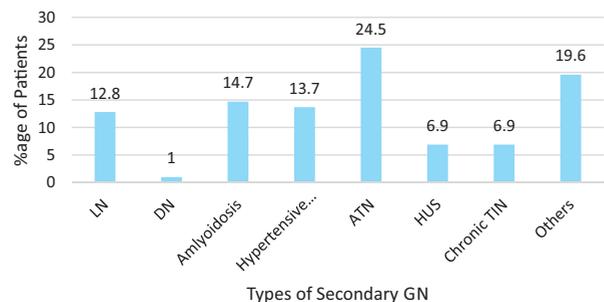


Figure-2. Distribution of secondary glomerular diseases and their percentages

LN= Lupus nephritis, DN= Diabetic nephropathy, ATN= Acute tubular necrosis, HUS=Haemolytic uremic syndrome, TIN= Tubulointerstitial nephritis

Distribution of glomerulonephritis according to age

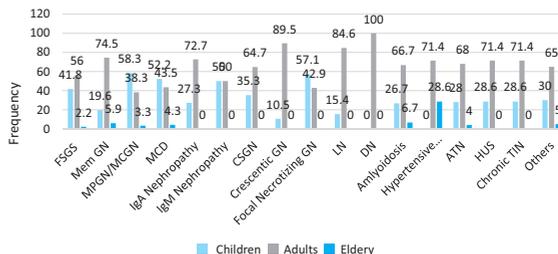


Figure-5. Age distribution of glomerular diseases

GN= Glomerulonephritis, FSGS= Focal segmental glomerulosclerosis, Mem= Membranous, MPGN= Membranoproliferative glomerulonephritis, MC= Mesangiocapillary, MCD= Minimal change disease, IgA= Immunoglobulin A, IgM= Immunoglobulin M, CS= Chronic sclerosing, LN= Lupus nephritis, DN= Diabetic nephropathy, ATN= Acute tubular necrosis, HUS=Haemolytic uremic syndrome, TIN= Tubulointerstitial nephritis

Gender-specific Distribution of Primary Glomerular Diseases

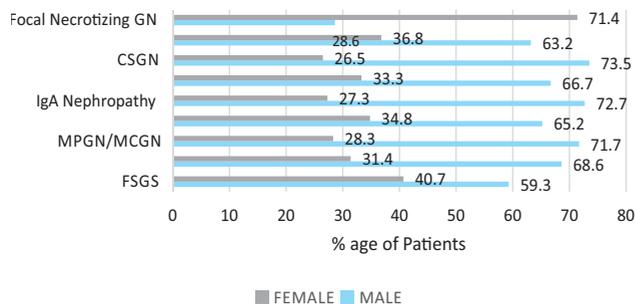


Figure-3. Gender distribution of primary glomerular diseases

GN= Glomerulonephritis, FSGS= Focal segmental glomerulosclerosis, Mem= Membranous, MPGN= Membranoproliferative glomerulonephritis, MC= Mesangiocapillary, MCD= Minimal change disease, IgA= Immunoglobulin A, IgM= Immunoglobulin M, CS= Chronic sclerosing,

DISCUSSION

Different types of Glomerulonephritis (GN) are the major cause of CKD throughout the world.<sup>1</sup> The types of GN in different populations vary according to race, region, gender, age and socioeconomic development.<sup>3</sup> The exact prevalence and incidence of CKD in Pakistan and India has not been estimated but the available data shows that chronic GN contributes almost one third cases leading to CKD. Apart from primary GN glomeruli are affected by infections, environmental factors and systemic diseases like diabetes and hypertension. With time the patterns of glomerular diseases is changing in different regions, races, ethnicities as demonstrated by different studies. These variations suggests the possibility of multiple factors contributing to the glomerulonephritis.<sup>7</sup> There is limited data on the

prevalence of different types of glomerulonephritis in Pakistan. A comparative reference of different related studies is given in the Table-II.

The results in our study revealed FSGS as the most common glomerular lesion among all types of GN. Recent analysis of renal biopsy specimen from several institutions in the United States revealed that over the past 20 years the incidence of focal segmental glomerulosclerosis (FSGS) has increased. Similarly, the incidence of FSGS has increased in Asia, Brazil and India, making it the most frequent reported PGN in some centres.<sup>11,12</sup> This is also in accordance with the experiences from Sudan and Saudi Arabia<sup>20,21</sup> and other studies conducted locally.<sup>22,23</sup> Regarding the regional discrepancies of primary GD described during a 6 years study from India FSGS accounted for 36.6% of primary GN followed by MN and MPGN.<sup>24</sup> Similarly, it was reported that the incidence of FSGS patients reaching CKD in the United States had increased by 11-folds during the past two decades. The increasing trend in the incidence of FSGS leading to CKD cases may be attributed due to changes in renal biopsy practices, in disease classification, and a real increase in the incidence of FSGS disease.<sup>13</sup> The FSGS is the most common GN in Brazil<sup>25</sup> India<sup>12</sup>, Bahrain<sup>26</sup>, second most common in Croatia<sup>27</sup>, and Sudan.<sup>28</sup> In contrast with these reports, the FSGS (8%) is the fourth most common GN in our study. It is interesting to point out that the second most common GN in our study is MPGN, similar to that of China<sup>3</sup>, Bahrain<sup>26</sup> Croatia<sup>27</sup>, and Sudan.<sup>28</sup>

The most common secondary GN in our study is ATN, responsible for AKI in our study. The frequent use of native herbal medications prescribed by Hakeem's, the use of non-steroidal anti-inflammatory drugs or the drugs used in the treatment of tuberculosis resulted in AKI which needed confirmation by renal biopsy in our study patients.

Amyloidosis and hypertensive nephropathy were the next frequent causes of secondary GN. The high prevalence of renal amyloidosis can be attributed to high prevalence of tuberculosis and other infections as described in different studies

from Pakistan and India. Amyloidosis is also among the common causes of NS in adults in this region and is secondary in nature in most of the cases. Commonly, renal amyloid were diagnosed on renal biopsy from patients having a history of tuberculosis and other chronic inflammatory diseases. High prevalence of secondary amyloidosis in our series may be due to the endemic nature of tuberculosis in this region.<sup>22</sup>

Chronic TIN and HUS are found to be less frequent. Tubulointerstitial and vascular diseases are less prevalent in our study as reported in some studies with similar indications for biopsy.<sup>1,4,11</sup> Most of these diseases are diagnosed using clinical grounds and other less invasive laboratory tests.<sup>11</sup> Although, the most common secondary GN worldwide is lupus nephritis (LN), but in the present study it is found to be less frequent.

There is a slight male predominance except in the case of LN, Focal Necrotizing GN and Chronic TIN. Male predominance also reported by Briganti et al.<sup>15</sup> Males have 1.5- to 2-fold greater risk of GN than females. Membranous GN can present as nephrotic syndrome and renal insufficiency. Some studies reported higher incidence in male while one study reported opposite.<sup>14,15</sup>

FSGS, MGN, IgA, CSGN and Crescentic GN are more common in adults. MPGN, MCD and Focal Necrotizing GN were the predominant primary GD in younger children. IgM nephropathy was equally common in both children and adults. Primary GD in elderly patients were FSGS, MGN, MPGN and MCD. In adults FSGS is becoming the leading cause of idiopathic nephrotic syndrome and being increasingly reported in children as well. The histologic spectrum of these is different in adults as compared with children as well as in tropical as compared with temperate countries. The peak age for FSGS leading to CKD incidence is 40 - 49 years among blacks while 70 - 79 years among white and Asian subjects. In our study, more than half of the FSGS is reported in adults followed by children, with lower proportion in elderly, which is in contrast to the above finding.<sup>13</sup>

## CONCLUSION

To conclude, a wide variation of major histological groups in the primary glomerular diseases has been observed. FSGS was the commonest primary GN, followed by MPGN and membranous GN. On comparison with other regional studies FSGS was the commonest primary GN in Pakistan and India, while in other countries membranous GN was more common. Primary GN was more common in adult group.

This study is a single-center experience. We were unable to analyze the data for the period before this due to inadequate data and poor standardization of the biopsy reporting. Another shortcoming of our study is the inability to perform EM (Electron Microscopy) in all cases which would have helped in better diagnosis. However, we feel that a relatively accurate diagnosis could be achieved in a majority of cases.

Being a single-center study, our findings do not reveal the spectrum of glomerular diseases in Pakistan. It is desirable to establish a single national renal biopsy registry so that data can be compared. Establishment of a national biopsy registry data would help to address differences in the spectrum of GD across the country and region. Widespread use of EM in all biopsies will go a long way in detecting rarer forms of GD; but for the meantime, a large proportion of centers have to manage without it due to lack of EM.

In short, the information in the present study is a valuable contribution for understanding the frequency of glomerulonephritis in the northwest province of Pakistan and may add to the available knowledge about this specific area of renal diseases. We hope that the data in this study will mark the outset for establishment of a national renal biopsy registry in our country.

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You miss 100% of the shots you don't take.



*“Lee Harvey Oswald”*

**AUTHORSHIP AND CONTRIBUTION DECLARATION**

Sr. #	Author-s Full Name	Contribution to the paper	Author=s Signature
1	Sultan Zafar Akhtar	Main idea, biopsy taking, manuscript writing, Review of the article as an expert nephrologist.	
2	Humera Adeeb	Assisted in biopsy taking, data collection, Manuscript writing, data analysis and references.	
3	Hajira Bibi	Data collection, data analysis and helped in manuscript writing.	
4	Ihsan Ullah	Evaluation of biopsy reports as pathologist, final review and correction of the manuscript, correspondence with the journal.	