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Research article

REVIEW OF RENAL BIOPSY DATABASE: A SINGLE CENTRE SOUTH INDIAN STUDY

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ABSTRACT

Background: The epidemiology of biopsy- proven renal disease (BPRD) provides information that is useful for clinical practice and investigation. India lacks a national renal data registry system and there is a scarcity of information on the pattern of BPRD in South India. **Objectives:** To determine the occurrence and analyse the epidemiology of BPRD in our local (South Indian) population. **Material and Methods:** A retrospective review of reports of native renal biopsies performed on patients at a tertiary care hospital in South India, from 2008 to 2013 was undertaken. All renal biopsies were studied by light and immunofluorescence microscopy and were classified into primary glomerulonephritis (PGN), secondary glomerulonephritis (SGN), tubulointerstitial nephritis, vascular nephropathy, hereditary nephritis, end stage renal disease and biopsies exhibiting no significant pathology. **Results:** A total of 661 cases were included in the study. The most common clinical syndrome as an indication for renal biopsy was NS (29%). PGN was the most common BPRD, accounting for 42.3 % of the cases. Minimal change disease (33.6%) was the commonest PGN followed by membranous nephropathy (15.7%) and focal segmental glomerulosclerosis (12.6%). Diabetic nephropathy (76.9%) was the commonest SGN (14.7%) followed by lupus nephritis. **Conclusion:** Our study represents an important contribution to understanding the epidemiology of renal disease in South India. The distribution pattern of PGN largely corresponds to the distribution pattern described in other South Indian studies. However, there is a wide variation of major histologic patterns of PGN across the world.

Keywords: Epidemiology, glomerulonephritis, nephritic syndrome, renal biopsy, renal disease.

INTRODUCTION

Renal biopsy is an established and vital procedure that is indispensable in the investigation and management of patients with renal disease.¹ The epidemiology of biopsy- proven renal disease (BPRD) provides critical insights about the occurrence of renal disease and this information is not only useful for clinical practice and investigation but

is vital for future research into renal disease. The prevalence of renal disease varies according to the geographic area, demography and race and is influenced by the socioeconomic conditions, prevalence of infectious diseases and indications for renal biopsy.^{2,3} Unlike certain regions, where community based renal biopsy registries exist, there

is no such documentation in India.^{4,6} Further there is scarcity of information on the pattern of renal disease in the native South Indian population.

The aim of the present study was to determine the occurrence and analyse the epidemiology of BPRD in a tertiary care hospital in South India.

MATERIAL AND METHODS

The records of all patients who underwent a renal biopsy at M. S Ramaiah Hospitals, Bangalore from September 2008 to September 2013 were retrospectively reviewed, after obtaining institutional ethical clearance. Information regarding patient's age, gender, indication of renal biopsy, underlying conditions associated with renal disease, laboratory investigations like serum creatinine, 24-hour urinary protein and serological data (Antinuclear antibodies, Antineutrophil cytoplasmic antibodies, anti-double stranded DNA, C3) were collected. Inadequate biopsies, a second biopsy in re-biopsy patients and renal allograft biopsies were excluded from the analysis.

The indications for renal biopsy were categorised into the following subgroups: nephrotic syndrome (NS), acute nephritic syndrome (ANS), acute renal failure (ARF), chronic renal failure (CRF), rapidly progressive renal failure (RPRF), asymptomatic urinary abnormality [non-nephrotic proteinuria (< 3.5 g/24 hr) [NNPU] or hematuria (≥ 3 red cells/high power field)] and hypertension with renal dysfunction.^{2,7} NS was defined as heavy proteinuria (> 3.5 g/24 hr or 4+ proteinuria) and serum albumin < 2.5 g/dL.^{2,4,8} The clinical diagnosis of ANS was made based on rapid onset of oedema, oliguria, hypertension, hematuria, mild to moderate proteinuria and reduced GFR.^{4,6} ARF was defined "as rapid (over hours to weeks) and usually reversible decline in GFR occurring, either in the setting of pre-existing normal renal function or with pre-existing renal disease" and RIFLE Criteria was followed to identify these cases.⁹ As per NKF KDOQI Guidelines, CRF was defined as either kidney damage (structural or functional abnormalities of the kidney manifest by either: Pathological abnormalities; or Markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests) or GFR < 60 mL/min/1.73 m² for 3 months.¹⁰ RPRF was defined as progressive renal impairment (deterioration of GFR, associated with

azotemia) over a period of few weeks, with presence of normal sized kidneys on ultrasonographic examination.¹¹

All the biopsy specimens were processed for light and immunofluorescence microscopy as per standard protocol by the same group of technicians and examined by the same group of pathologists. For light microscopy, 3- 4 μ m thick sections were stained with Hematoxylin and Eosin, Masson's trichrome, periodic acid Schiff and Jones silver methanamine. Special stains (Congo red) were used when warranted. Immunofluorescence study was done using fluorescein isothiocyanate (FITC) conjugated rabbit anti-human immunoglobulin (Ig) G, IgM, IgA, and C3 antibodies from Biogenex. The final diagnosis was made for each case on the basis of both clinical and histological investigations. Histological categories were classified as follows: i) Primary glomerulonephritis (PGN) which included 8 groups – minimal change disease (MCD), membranous nephropathy (MN), focal and segmental glomerulosclerosis (FSGS), membranoproliferative glomerulonephritis (MPGN), chronic glomerulonephritis (CGN), Crescentic glomerulonephritis (CreGN), Diffuse proliferative glomerulonephritis (DPGN) and IgA nephropathy (IgAN); ii) Secondary glomerulonephritis (SGN) which included 8 groups- diabetic nephropathy (DN), lupus nephritis (LN), amyloidosis, Goodpasture syndrome (GPS), Henoch-Schonlein purpura (HSP), light chain deposit disease (LCDD), haemolytic- uremic syndrome (HUS)/ thrombotic microangiopathy (TMA) and rheumatoid arthritis (RA); iii) Tubulointerstitial nephritis (TIN) which included acute TIN, chronic TIN, acute kidney injury/ acute tubular necrosis (AKI/ATN), myeloma cast nephropathy, nephrocalcinosis, juvenile nephronophthisis, granulomatous interstitial nephritis, analgesic nephropathy and systemic sclerosis; iv) Vascular nephropathy (VN) which included benign nephrosclerosis (BNS), malignant nephrosclerosis (MNS), vasculitis and renal cortical necrosis (RCN); v) Hereditary nephritis comprising of Alport syndrome; vi) End stage renal disease (ESRD), which included biopsies exhibiting severe interstitial fibrosis and tubular atrophy with advanced glomerulosclerosis and arteriosclerosis, and vii) Biopsies exhibiting no significant pathology.

Statistical analysis: The incidence of each type of renal disease and biopsy indication were computed.

Quantitative data were expressed as mean or median. Qualitative data were expressed as numbers and percentages.

RESULTS

Of 752 cases analysed, 91 cases comprising of 72 renal allograft biopsies and 19 inadequate biopsies were excluded. The remaining 661 cases, included in the study had a male: female ratio of 1.66 with a mean age of 42.8 years and a range of 8 months to 78 years.

The number of biopsies performed each year increased annually as depicted in Figure 1.

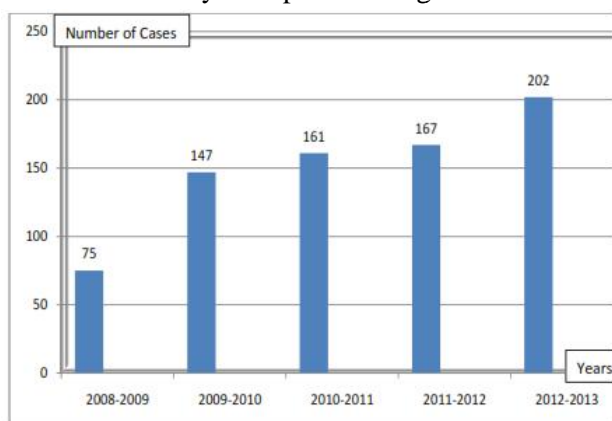


Fig1: Renal biopsies performed each year.

Table 1 Clinical indications of renal biopsy

Table 2: Distribution of glomerular disease by age

Disease	< 10	10-20	21-30	31-40	41-50	51-60	61-70	71-80	Median age
MCD	25	14	19	15	11	6	6	0	25
MN	0	3	14	8	8	8	4	0	32.5
FSGS	2	5	9	6	4	6	4	0	35.8
MPGN	0	3	5	8	6	5	0	0	32.5
CGN	0	3	5	5	4	3	2	1	32
CreGN	0	5	5	3	4	1	3	0	36.7
DPGN	4	6	2	4	2	0	2	0	32.5
IgA N	0	1	4	7	3	2	0	1	35
DN	0	0	1	16	18	39	31	5	54.7
LN	0	6	7	7	0	1	0	0	24.3
Amyloidosis	0	0	0	0	1	0	1	0	-

The distribution and frequency of different renal diseases are shown in Table 3. PGN accounted for 42.3% of the cases and was the most common BPRD. MCD was the commonest PGN followed by

Clinical Diagnosis	Number of renal biopsies *(percentages)
NS	192 (29%)
CRF	120 (18.2%)
ARF	99 (14.9%)
RPRF	70 (10.6%)
Non-nephrotic proteinuria	66 (10%)
Hypertension with renal dysfunction	52 (7.9%)
ANS	40 (6.1%)
Hematuria	22 (3.3%)
Total	661 (100%)

*Only the first renal biopsy in each case was considered.

The clinical indications for renal biopsy are depicted in Table 1 with NS being the commonest followed by CRF.

Table 2 shows the clinical syndrome associated with each histological category. The most common cause of NS was MCD followed by MN and FSGS and the most common cause of ANS was DPGN followed by MPGN. The most frequent causes of CRF, ARF, RPRF, NNPU and hematuria respectively were Chronic TIN, Acute TIN, CreGN, DN and IgAN.

The distribution of glomerular disease by age is shown in Table 4. Most of the PGN were diagnosed between 2nd and 3rd decade

MN. The most common SGN was DN. The most common TIN was chronic TIN followed by acute TIN and the most common VN was BNS.

Table3: Clinical presentation of each histological category

Histological Diagnosis	NS	CRF	ARF	RPRF	NNPU	Hypertension	ANS	Hematuria	Total
MCD	89 (46.4)	2(1.7)	1(1.0)	-	4(6.1)	-	-	-	96
MN	38 (19.8)	3(2.5)	-	-	4(6.1)	-	-	-	45
FSGS	22(11.5)	4(3.3)	1(1.0)	1(1.4)	7(10.6)	-	1(2.5)	-	36
MPGN	8(4.2)	3(2.5)	-	7(10.0)	1(1.5)	-	8(20)	-	27
CGN	-	14(11.7)	2(2.0)	3(4.3)	1(1.5)	2(3.8)	1(2.5)	-	23
CreGN	-	1(0.8)	1(1.0)	16(22.9)	-	-	3(7.5)	-	21
DPGN	4(2.1)	-	1(1.0)	4(5.7)	-	1(1.9)	10(25)	-	20
IgAN	3(1.6)	2(1.7)	-	2(2.9)	1(1.5)	-	3(7.5)	7(31.8)	18
DN	17(8.9)	23(19.2)	19(19.2)	3(4.3)	21(31.8)	18(34.6)	5(12.5)	4(18.2)	110
LN	8(4.2)	2(1.7)	-	3(4.3)	1(1.5)	-	6(15)	1(4.5)	21
Amyloidosis	2(1.0)	-	-	-	-	-	-	-	2
HUS/TMA	-	-	2(2.0)	-	-	-	-	-	2
GPS	-	-	-	2(2.9)	-	-	-	-	2
RA	-	-	-	-	2(3.0)	-	-	-	2
HSP	-	-	1(1.0)	-	1(1.5)	-	-	-	2
LCDD	-	1(0.8)	1(1.0)	-	-	-	-	-	2
Congenital	-	-	1(1.0)	-	-	-	-	-	1
Alport	-	-	-	-	-	-	-	1(4.5)	1
AcuteTIN	-	6(5.0)	20(20.2)	5(7.1)	6(9.1)	6(11.5)	2(5.0)	1(4.5)	46
ChronicTIN	-	33(27.5)	9(9.1)	6(8.6)	7(10.6)	6(11.5)	-	2(9.1)	63
Analgesic	-	3(2.5)	1(1.0)	-	-	-	-	-	4
Granuloma	-	1(0.8)	-	-	-	-	-	-	1
AKI/ATN	-	-	10(10.1)	3(4.3)	-	-	-	-	13
Myeloma cast Nephropathy	-	1(0.8)	1(1.0)	-	-	-	-	-	2
Medullary Nephronopthisis	-	-	1(1.0)	-	-	-	-	-	1
Systemic Sclerosis	-	-	1(1.0)	-	-	-	-	-	1
Nephrocalcinosis	-	-	1(1.0)	-	-	-	-	-	1
BNS	-	11(9.2)	1(1.0)	-	-	14(26.9)	-	-	26
MNS	-	1(0.8)	2(2.0)	5(7.1)	-	-	-	-	8
RCN	-	-	-	2(2.9)	-	-	-	-	2
Vasculitis	-	-	2(2.0)	1(1.4)	-	-	-	-	3
ESRD	1(0.5)	9(7.5)	1(1.0)	4(5.7)	1(1.5)	-	1(2.5)	-	17
No signif	-	-	19(19.2)	3(4.3)	9(13.6)	5(9.6)	-	6(27.3)	42
Total	192	120	99	70	66	52	40	22	661

Hypertension=hypertension with raised renal parameters; No signif= No significant pathology. Figures in parenthesis represent percentage of that particular clinical presentation.

DISCUSSION

This report provides comprehensive information about the occurrence, demographics and clinical syndromes of renal diseases diagnosed by renal biopsy, over a period of five years in a single tertiary care centre in South India. The study reflects the pattern and prevalence of BPRD of moderate to severe intensity rather than the true prevalence of the disease, as only those with significant disease severity are likely to be biopsied.

Table 5 demonstrates the comparison of our basic data with other published studies. Similar to the majority of other published studies worldwide, PGN was the most predominant renal disease in our study, followed by SGN and TIN.^{3,5,7,8,12-19} The hereditary and vascular nephropathies were less frequent in majority of the studies.

Table 4: Comparison of our basic data with other published studies

Variables	Present study	Hyderabad ¹	Pakistan ¹³	Oman ¹⁴	Bahrain ¹⁵	Estonia ¹⁶	Germany ¹⁷	Serbia ⁸	Italy ³	Brazil ¹⁸	Morocco ¹	Romania ¹⁹	Korea ²	Vellore ¹²
Duration	2008-2013	1990-2008	1995-2008	1999-2010	1990-2002	2000-2010	1983-2006	1987-2006	1996-2000	1993-2007	2000-2007	2005-2010	1987-2006	1986-2002
Total no	661	1849	1793	424	490	578	359	2362	14607	9617	161	239	1818	5415
M:F	1.66:1	1.5:1	1.6:1	-	-	-	1.55:1	1.05:1		0.96:1	1.68:1	1.41:1	1:1	-
Mean age	42.8	32.3 +/-18.4	32.9 +/-12.8	-	-	39.9+/-17.9	51.8	39.1+/-13.8		35.1 +/-18.7	40.4 +/-15	41.9 +/-2.8	36	-
PGN*	42.3	69.1	73	69.1	44.8	45.4	51	64.2	64.3	51	52	55.3	74	71
SGN**	21.6	18.2	10.9	30.9	33.6	22.3	28	25	24.7	22.6	33	39.1	11.8	-
TIN*	20	6.7	11.6	-	13.1	8.2	9	3	5.3	2.2	-	3.3	-	3.6
VN*	6	3.2	3.9	-	-	-	12	4.4	4.7	3.9	-	0.9	-	-
MCD**	33.6	21.8	7.9	24.6	30	14.1	16	7.8	7	15.5	26	2.6	20.9	16
MN**	15.7	10	23.5	17.7	13.5	-	14	18.9	25	20.7	23	27.6	16.7	13.8
FSGS**	12.6	15.3	29	30.7	23.8	16.1	13	18.9	15	24.6	9.4	17.2	7.5	24
MPGN**	9.4	7.5	1.5	2	14.3	7.7	7	10	6	4.2	17	29.3	5.3	5.2
CGN**	8	7.5	16	-	-	-	-	-	-	1.7	-	11.2	-	-
CreGN**	7.3	6.5	5.3	-	2.7	-	8	5.1	4	1.7	6	9.5	-	-
DPGN(including PIGN)**	7	14.6	-	6.5	3	-	-	2	4	5.4	4.5	-	-	-
IgAN**	6.3	6.3	2.1	11.9	0.4	35.5	26	12.2	31	20.1	12	13.8	38.2	12.1
Non IgA MGN**	0	7.5	2.6	-	5.8	-	17	25.1	11	5.2	1.1	-	0	28.4
DN***	76.9	6.5	8.1	-	31.9	-	25	-	15	10.1	15	-	23.4	-
LN ***	14.7	80.1	44.1	98.5	38.9	-	-	75	20	42.4	45	26.6	74	-
Amyloidosis***	1.2	8	42.1	1.5	2.7	-	-	6.4	20	6.2	19	10	-	-

*These figures represent percent of total renal disease; ** these figures represent percentage calculated out of total PGN; ***these figures represent percentage calculated out of total SGN; PIGN= Post infectious glomerulonephritis; Non IgA MGN= Non IgA Mesangioproliferative glomerulonephritis.

Similar to other studies around the world, including South India, NS was the most frequent indication for renal biopsy accounting for 29% of the cases.^{3,7,8,12,13,18} However, asymptomatic urinary abnormality was found to be more frequent in the Italian registry and Japanese study, perhaps reflecting a greater tendency to biopsy asymptomatic proteinuria and hematuria.^{4,5,7}

Our gender distribution with male predominance was similar to many other epidemiological studies.^{3,7,12,13,17,19} however, gender distribution was balanced in Brazilian, Serbian and Korean studies.^{2,8,18} This partly may be explained by the higher relative frequency of LN, which occurs more frequently in women, in the latter studies.

MCD, MN and FSGS have been the three most frequently diagnosed PGN, comprising 69.1% of the latter. MCD was the commonest PGN and commonest cause of NS in our study, which is in concordance with another South Indian study

(Hyderabad) and other studies from Morocco and Bahrain.^{2,7,15} MCD exhibits variable geographic distribution, European studies and a South Indian study conducted at Vellore have shown a decline in the relative frequency of MCD.^{5,8,12,19} It is the most common cause of NS in children, with 80% of histological verified cases occurring in children < 6 years and a male: female (M:F) ratio of 2:1.²⁰ In our study, MCD comprised 33.6% of PGN, peaked in the first decade of life and was more common in males (M: F, 1.6:1).

MN is cited as the most common cause of adult NS in most widely used renal pathology text books.^{7,8,20} In our study it was the second most frequent PGN (15.7%) and most common cause of NS in adults with peak incidence in the third and fourth decades of life and a M:F ratio of 1.1:1. There is a worldwide increase in the incidence of FSGS, which has become the main cause of NS instead of MN, especially in countries with preponderant black and Hispanic

Americans.^{3, 8,21} However, in many European countries (Italy and Serbia) and United Arab Emirates (UAE), it is still common and prevails as the commonest cause of NS.^{5,8}

The prevalence of FSGS has increased from <10% to 25% of PGN in the past 20 years.²² New environmental causes and broadened morphological definition of FSGS may partly explain this increasing trend.^{21,23} It was the third commonest PGN (12.6%) in our study. Two other South Indian studies conducted at Vellore and Hyderabad have reported FSGS as the second commonest PGN and studies from Pakistan, Brazil and Arab countries have quoted it as the commonest PGN.^{3,12,13,14,18} The disease is relatively more common in adults and males (M:F, 1.4:1) with 44% to 74% presenting as NS.²³ In our study the peak age at presentation was third decade and 61% of FSGS cases presented with NS with M: F ratio of 2.3:1.

IgA nephropathy was the least frequent PGN (6.3%) in our study, a pattern similar to other South Indian studies, some South Asian (Pakistan) and West Asian studies (Iran and Bahrain).^{3,12,13,15,22} However, it is the commonest PGN in Europe, Estonia, West Germany and some East Asian countries (Japan, Korea).^{2,4,5,16,17, 21} Even though it is considered as the most common glomerular disease worldwide, its detection rate varies depending on biopsy indications and mass urinary screening programs for asymptomatic urinary abnormalities.^{2,7} Further high prevalence in certain populations may be related to genetic background.²

A decreasing incidence of MPGN has been reported in different parts of the world probably due to improved socioeconomic conditions and reduction in the regional endemic diseases.^{3,15,18} However, it was the second commonest PGN in a study conducted in Nepal and a high frequency was found in Romania, attributable to the higher prevalence of infectious diseases like streptococcal infection and Hepatitis B and C.^{19,24} In our study MPGN comprised 9.4% of all PGN, which is slightly higher compared to other South Indian studies conducted at Vellore (5.2%) and Hyderabad (7.5%).^{3,12}

The commonest SGN in our study was DN comprising 77% of all SGN, followed by LN. In the many studies worldwide, including East and West Asian, European, South American and Arab countries, LN was the most frequent SGN and the

prevalence of DN was low.^{2,7,8,14,15,18,19} This variation is due to different selection criteria for renal biopsy in these patients. In the absence of clinical data suggestive of another disease (Non-diabetic renal disease, NDRD), DN is usually diagnosed without a renal biopsy, further, patients with superimposed retinopathy and long disease duration are generally not considered for biopsy irrespective of the severity of renal syndromes.^{2,8} Given the relatively higher prevalence of NDRD in our set up, we adopt a more liberalised biopsy procedure and all diabetics, irrespective of presence or absence of retinopathy and disease duration, with the slightest clinical suspicion of superimposed NDRD are biopsied.²⁵

Certain studies from Pakistan and UAE have reported a high frequency of amyloidosis. However, despite the higher prevalence of tuberculosis and other infectious diseases, amyloidosis comprised only 1.2% of SGN in our study. This is because the disease is confirmed in suspected cases by gingival or abdominal fat pad biopsies rather than renal biopsy.

TIN are generally diagnosed based on clinical data and other less invasive procedures rather than renal biopsy, accounting for their less frequency in many studies.⁸ Compared to the other two South Indian studies, our study shows a relatively high frequency of TIN (20% of BPRD). This is because we biopsy these cases more frequently as we believe that i) TIN and other renal diseases with renal failure/insufficiency cannot be often differentiated based on clinical and laboratory data ii) with an early diagnosis most acute TIN can be successfully treated and iii) delayed diagnosis leading to delayed treatment of acute TIN, may lead to interstitial fibrosis.

Drawing accurate conclusions from and making comparisons with other published studies from same and different countries was difficult, as there were several biases related to racial and geographic characteristics, renal biopsy indications, different patho-physiological classifications and categorisation of clinical syndromes.

CONCLUSION

We have documented the demographics of BPRD in our South Indian patient population. The distribution pattern of PGN largely corresponds to the distribution pattern described in other South Indian studies. However, there is a wide variation of major histologic patterns of PGN across the world. Our study

represents an important contribution to understanding the epidemiology of renal disease in South India. Finally, in order to obtain an accurate overview of the epidemiology of BPRD in our country, it is imperative to maintain a national registry with participation from the many Nephrology Centers.

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