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ORIGINAL RESEARCH ARTICLE

# CLINICO-PATHOLOGICAL SPECTRUM OF BIOPSY PROVEN NATIVE KIDNEY DISEASE IN A TERTIARY HOSPITAL IN NEPAL

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## ABSTRACT

**Background**: Kidney biopsy has been regarded as an important tool for the diagnosis, management and monitoring the prognosis of renal diseases. We conducted this study to find out the clinico-pathological spectrum by native kidney biopsy in a relatively large scale.

**Methods:** This was a hospital based, prospective, observational study carried out in a tertiary hospital of Kathmandu from January 2022 to December 2023. The biopsy specimens were reported by nephropathologists on the basis of light microscopy, direct immunofluorescence for all samples and electron microscopic examination whenever indicated. The patient`s demographic profile, indication and histological findings of kidney biopsy were studied and analyzed using appropriate statistical tools.

**Results:** A total of 610 kidney biopsies were performed during the study period, of which 24 samples did not meet the inclusion criteria and 586 patients were included in the final analysis. The mean age of the patients was 42.08 ±9.09 years and 59.03% of the patients were younger than 40 years. Females outnumbered the males with female to male ratio of 1.09. The most common presentation was limb swelling (81.22%) and nephrotic syndrome was the most common indication for the biopsy and the most common histological finding was lupus nephritis, followed by IgA nephropathy and FSGS. Non-diabetic kidney disease was found in 54.28% of diabetic patients who underwent biopsy.

**Conclusions:** Nephrotic syndrome was the most common indication for kidney biopsy with lupus nephritis being the most common histological finding. Non diabetic kidney disease (NDKD) was found in more than half of the patients with diabetes mellitus.

## INTRODUCTION

Despite advances in non-invasive biochemical and imaging investigations, kidney biopsy remains an important tool in clinical nephrology. The introduction of the kidney biopsy is one of the major events in the history of nephrology. It helps to diagnose and ascertain the degree of active and chronic changes that would be helpful to prognosticate the underlying diseases and to decide the treatment modalities.

Reports have revealed that the spectrum of histological findings of native kidney biopsy reports vary geographically and this fact applies to our part of the world too. Due to the lack of central registry system of kidney biopsy in our country, there does not seem to have a uniformity in the presentation and reporting of histological patterns of native kidney diseases. Bir hospital is one of the largest tertiary hospital in the country with significantly bigger geographic spectrum and number of patients getting Nephrology service. The annual report of Bir Hospital revealed that OPD service was provided to a total of 18,706 visits in one fiscal year of 2022/23.[1] There is a trend of offering kidney biopsy to all indicated patients with a relatively less threshold in our hospital.

Although there has not been major change in the trends and techniques of kidney biopsy, introduction of electron microscopy as a routine part of histopathologic study for the last few years has contributed significantly to the diagnostic and prognostic implications. We noticed a paucity of data after introduction of electron microscopic examination of biopsy samples on a routine basis. So, we conducted a prospective study to analyze the histopathologic presentation of kidney biopsy over a period of two years in a tertiary hospital of Nepal.

## METHODS

This was a hospital based, prospective, observational study carried out in the Department of Nephrology of Bir Hospital, Kathmandu over a period of two years from January 2022 to December 2023. All consecutive kidney biopsies done during the study period were included. All patients who had an indication to do kidney biopsy were counseled by the treating nephrologist and a written consent was obtained prior to the procedure. Patients who had contraindication for renal biopsy (small sized kidneys with loss of cortico-medullary differentiation, single functioning kidney, polycystic kidney

**Table 1: Important baseline characteristics of the patients**

| Glomerular disease | Age (Years) | Male sex (%) | Hematuria (%) | Limb swelling (%) | Serum Cr. (mean±SD mg/dL) | Serum Alb (mean±SD mg/dL) | Spot urine ACR (mg/mg) |
|---|---|---|---|---|---|---|---|
| **FSGS** | 41.78 | 44 | 46 | 99 | 2.0±1.34 | 2.3±1.9 | 5.6±4.7 |
| **IgA Nephropathy** | 38.36 | 40 | 96 | 87 | 2.58±1.92 | 3.4±2.1 | 2.5±2.1 |
| **LN** | 30.83 | 8.6 | 35 | 79.48 | 1.59±1.56 | 3.2±1.78 | 3.2±1.9 |
| **MN** | 44.55 | 45 | 37 | 98.7 | 1.39±0.87 | 1.9±1.3 | 6.7±4.8 |
| **MCD** | 34.16 | 62 | 2.4 | 100 | 1.54±1.29 | 1.8±1.34 | 6.5±5.7 |
| **ATIN** | 32.4 | 56 | 12.4 | 53.2 | 2.45±1.98 | 3.9±2.3 | 0.6±0.2 |
| **AAV** | 61 | 23 | 100 | 56.7 | 3.67±1.92 | 3.4±2.2 | 2.2±1.5 |
| **DKD** | 55.19 | 53 | 12.7 | 97.8 | 2.2±1.28 | 2.9±1.8 | 3.8±2.7 |
| **PIGN** | 40.2 | 76 | 100 | 34.6 | 3.22±1.32 | 3.6±2.7 | 1.4±0.9 |
| **C3 GN** | 49 | 56 | 79 | 67.8 | 2.34±1.67 | 3.5±2.9 | 1.5±1.1 |
| **Amyloidosis** | 51 | 62 | 14.2 | 95.4 | 1.78±0.89 | 2.0±1.4 | 5.7±4.3 |
| **C1q N** | 32.25 | 56 | 24.7 | 78.5 | 2.1±1.92 | 3.3±2.6 | 1.6±1.12 |

*AAV- ANCA associated vasculitis, ATIN- Acute tubulointerstitial nephritis, C1q N- C1q associated nephropathy, C3 GN- C3 associated glomerulonephritis, DKD- diabetic kidney disease, FSGS- focal segmental glomerulosclerosis, LN- lupus nephritis, MCD- minimal change disease, MN- membranous nephropathy, PIGN- post streptococcal glomerulonephritis.*

disease and those with hydronephrosis), had insufficient biopsy specimens and who had allograft biopsies were excluded from the study.

Those who were on antiplatelet or anticoagulants were biopsied after the discontinuation of the drug and appropriate time interval. Blood pressure was adequately controlled before biopsy in those patients who were taking antihypertensive drugs. All biopsies were conducted under ultrasonography (USG) guidance with the use of local anesthesia. A self-adjustable, automated, spring-loaded biopsy (needle) gun of 16 to 18 G size was used for the biopsy. The specimen was collected for light microscopy and immunofluorescence for all patients and for electron microscopy when clinically indicated. Sample was sent in 10% formalin for light microscopy, in Michel's transport media for immunofluorescence and 3% glutaraldehyde for electron microscopy.

After the biopsy, the patients were kept admitted overnight for observation and were monitored for the possible complications. Those who had macroscopic hematuria were monitored with repeat complete blood count and ultrasound of the abdomen and pelvis. Those who had developed significant hematuria were managed with blood transfusion and were discharged only when the urine was clear.

The samples were analyzed by the nephropathologists either at Lal pathlabs in India or Pratham Laboratories in Kathmandu. Light microscopic examination and direct immunofluorescence tests were done for all patients and electron microscopic examination was done when clinically indicated.

The details on demographic profiles of patients, indications for kidney biopsy, baseline clinical and renal parameters, and complications encountered after biopsy and histological patterns were recorded. The data were first entered in the MS excel sheet, which were later transferred to SPSS version 20 (Chicago, IL, USA) for analysis. The data were analyzed using appropriate statistical tools. The continuous variables were expressed as mean ± standard deviation (SD) and ratio. The categorical variables were expressed as frequency and percentage. Ethical approval from the institutional review board (IRB) of National Academy of Medical Sciences (NAMS) was taken prior to the beginning of the study.

## RESULTS

A total of 610 kidney biopsies were performed during the study period. With working days of 482 during the study period, in an average 1.48 biopsies were done per day and 44.4 biopsies per month.

Among all biopsies, allograft biopsies were 22 and rest of 588 were the native kidney biopsies. Among native kidney biopsies, sample was insufficient in 2 biopsies. So, a total of 586 biopsy reports were included for the final analysis. (Fig.1) Electron microscopic (EM) evaluation was done in 392 (66.89%) patients.

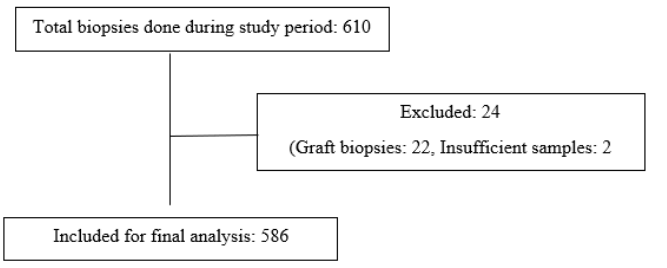


**Figure 1: Flow chart of the study**

Mean age of the patients was 42.08 ±9.09 years (Minimum 14 years, maximum 78 years). Males were 280 (47.79%) and females were 306 (52.21%) with female to male ratio of 1.09.

Limb edema was present in 81.22% and hematuria in 49.72% of

the patients. Average baseline serum creatinine of all studied patients was 3.3±3.05 mg/dL (Range 0.5 to 15.9 mg/dL). The highest mean creatinine was found among patients with anti-glomerular basement membrane disease (11.73±3.8 mg/dL) followed by ANCA associated vasculitis (3.67±1.92 mg/dL) and Post infectious nephropathy (3.22±1.32 mg/dL).

Mean baseline serum albumin was 2.84±2.0 mg/dL. The lowest serum albumin was seen in patients with minimal change disease (1.8±1.34 mg/dL) followed by membranous nephropathy (1.9±1.3 mg/dL).

Mean baseline spot urine albumin creatinine ration (ACR) was 3.7±2.8 mg/mg with the highest value among patients with MN (6.7±4.8 mg/mg) followed by MCD (6.5±5.7 mg/mg) (Table 1).

Majority of the patients (44.19%) were in the age group of 21 to 40 years followed by 41 to 60 years (30.54%) (Table 2).

**Table 2: Age and sex-wise distribution of patients**

| Age (in years) | Male n (%) | Female n (%) | Total n (%) |
|---|---|---|---|
| **< 20** | 44 (15.72) | 43 (14.05) | 87 (14.84) |
| **21-40** | 124 (44.28) | 135 (44.11) | 259 (44.19) |
| **41-60** | 84 (30) | 95 (31.05) | 179 (30.54) |
| **>60** | 28 (10) | 33 (10.79) | 61 (10.40) |
| **Total** | 280 | 306 | 586 (100) |

The most common clinical presentation was limb swelling (47.7%). Other common symptoms were generalized anasarca (34%), oliguria (12%), dyspnea (7.4) and skin rashes (5.4%) (Table 3).

**Table 3: Symptomatic presentation of the patients**

| Symptoms | Frequency (%) |
|---|---|
| Limb swelling | 476 (81.22) |
| Generalized body swelling | 199 (34) |
| Oliguria | 70 (12) |
| Dyspnea | 43 (7.4) |
| Skin rashes | 32 (5.4) |
| Joint pain | 28 (4.8) |
| Fever | 25 (4.3) |
| Throat pain | 20 (3.5) |
| Gross hematuria | 16 (2.8) |

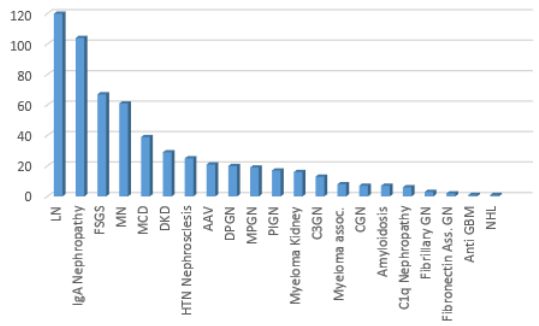


**Figure 2: Frequency of glomerular diseases on kidney biopsy**

The most commonly found glomerular disease on kidney biopsy was lupus nephritis (20%) followed by IgA Nephropathy (18%), focal segmental glomerulosclerosis (FSGS) (11%) and membranous nephropathy (10%) (Figure 2).

The most common syndromic presentation having indication for performing kidney biopsy was nephrotic syndrome (39.07%) followed by lupus nephritis (23.03%) and acute nephritic syndrome (14.16%). Rapidly progressive glomerulonephritis (RPGN) was the indication of kidney biopsy in 8% of patients. (Table 4) Among patients with lupus nephritis, repeat biopsy was done for 5 patients, the main indications for which were LN flares and poor response to treatment. Two patients had switching of class, one had thrombotic micro angiopathy and two had significant chronicity.

**Table 4: Indication for kidney biopsy**

| Indication for kidney biopsy | Number (%) |
|---|---|
| Nephrotic syndrome | 229 (39.07%) |
| Lupus nephritis | 135 (23.03%) |
| Acute nephritic syndrome | 83 (14.16%) |
| Rapidly progressive glomerulonephritis | 47 (8%) |
| Unexplained renal impairment | 44 (7.5%) |
| Diabetes with suspicion of non-diabetic kidney disease | 31 (5.3%) |
| Microscopic hematuria | 17 (2.94%) |

Altogether 6.4% (n=38) of the patients required hemodialysis support for their renal impairment and 1.1% required maintenance renal replacement therapy.

A total of 35 patients with diabetes mellitus had undergone kidney biopsy. The most common indication for biopsy was recent and rapid rise in the proteinuria (35%), acute on chronic kidney disease (25%), active urinary sediments (22%) and acute kidney injury (18%). Non-diabetic kidney disease (NDKD) was found in 19 (54.28%) patients (In combination with diabetic kidney disease in 14 (40%) and isolated non-diabetic kidney disease in 5 (14.28%) patients. Most common form of NDKD found in the patients with diabetes was acute tubulointerstitial nephritis (36.84%) followed by membranous nephropathy (26.31%) and FSGS (19.8%). (Table 5)

**Table 5: Patterns of nondiabetic histological findings in diabetic patients (n=19)**

| Renal biopsy findings | NDKD & DKD | NDKD only | Total |
|---|---|---|---|
| ATIN | 4 (21.07%) | 2 (10.52%) | 6 (31.59%) |
| MN | 3 (15.78%) | 1 (5.26%) | 4 (21.07%) |
| FSGS | 3 (15.78%) | 0 | 3 (15.78%) |
| IgA Nephrop-athy | 1 (5.26%) | 1 (5.26%) | 2 (10.52%) |
| CIN | 2 (10.52%) | 0 | 2 (10.52%) |
| Crescentic GN | 0 | 1 (5.26%) | 1 (5.26%) |
| TMA | 1 (5.26%) | 0 | 1 (5.26%) |

*ATIN- Acute tubulointerstitial nephritis, FSGS- focal segmental glomerulosclerosis, CIN- chronic interstitial nephritis, MN- membranous nephropathy, TMA- thrombotic microangiopathy*

## DISCUSSION

Ours being the Government run tertiary hospital and getting patients referred from all over the country, we performed significantly larger number of biopsies compared to other series in the country.[2, 3] Similarly, the spectrum of findings on biopsy was also of widely varied that ranged from different forms of glomerular diseases to fibronectin associated nephropathy, fibrillary glomerulonephritis, myeloma associated glomerular diseases and one case of non-hodgkin's lymphoma (NHL) associated renal pathology.

Majority of the patients in our study were of age less than 40 years, suggesting that renal diseases were common problem of young age. This finding is consistent with other studies done in different centers of the country.[2-4] Relatively, we had a lesser proportion of pediatric patients who had undergone kidney biopsy. The reason behind it could be the absence of pediatric nephrologist in our center and all the patients in pediatric age group being referred to the children's hospital available nearby to our center. Additionally, there are limited spectrum of renal and glomerular diseases that requires kidney biopsy as most of the childhood nephrotic syndrome is managed with corticosteroids without the necessity of kidney biopsy. Similar findings were reported in other studies.[2, 5, 6]

There are many indications for native kidney biopsy like unexplained renal failure, acute nephritic syndrome, nephrotic syndrome, isolated glomerular hematuria, connective-tissue diseases (eg, systemic lupus erythematosus). The most common indication for kidney biopsy in our study was nephrotic syndrome (39.07%), which is consistent with the findings in many other studies.[7-10] Lupus nephritis was the another important indication for doing kidney biopsy. Although lupus nephritis can be managed without the strict indication of kidney biopsy, it is mandatory to classify it as per the histological classes to initiate and monitor the immunosuppressive treatment. On top of that repeat biopsies are indicated to certain patients who won't respond to treatment and have proteinuric flares of the disease despite treatment and also to identify the significant chronicity that would be helpful to decide whether to continue or quit the immunosuppressive medications.

Diabetes mellitus (DM) has been considered as the commonest cause of CKD.[11,12] Conventionally, it used to be considered as the sole cause of proteinuria and renal impairment in a patient with DM. However, this concept has been changed in the recent years and the co-existence of non-diabetic kidney disease in a patient with diabetes needs to be ruled out by doing kidney biopsy in suspected cases. DKD is not the only form of renal disease in patients with DM, but other non-diabetic renal diseases can occur: glomerular (membranous nephropathy), tubulointerstitial or vascular diseases. In this study, kidney biopsy was done for 35 patients with the history of DM, of which 54.28% patients were found to have non-diabetic kidney disease (NDKD). Isolated non-diabetic kidney disease were found in 14.28% patients with DM. This finding would further highlight the necessity of high index of suspicion of NDKD in patients with DM. Similar findings were reported in few other studies too.[13-16] The common NDKD in patients with DM were acute tubulointerstitial disease (ATIN) followed by MN, FSGS and IgAN, which is of not much different from few other studies.[17]

The most common glomerular disease found in this study was lupus nephritis (20%) followed by IgA Nephropathy (18%). This finding is different from few other studies from both inside and outside the country. In a recent study done by Ghimire et al, MN was the most common pattern of glomerular disease.[2] FSGS was reported as the most common finding by Rathi et al.[18] It's quite difficult to pinpoint the specific reason for the difference in the pattern of glomerular injury in different studies but one of the reasons we could speculate is that ours being the tertiary center located in the central part of the country would receive the varieties of cases from all over the country.

Due to the lack of renal registry system in our country, it's quite difficult to gather and compile the information regarding kidney disease and in particular the histological findings on kidney biopsy on National level. Despite these limitations, studies like this would be helpful to identify the major histological findings of glomerular and non-glomerular kidney diseases. One of the limitations of this study was that it was a single center observational study that would limit the number and variations of histological findings.

## CONCLUSION

Our study attempted to generate information about biopsy proven renal diseases from central Nepal that would be helpful not only for the patients but also for the policy makers. Nephrotic syndrome was the most common indication for kidney biopsy with lupus nephritis being the most common histological finding. Non diabetic kidney disease (NDKD) was found in more than half of the patients with diabetes mellitus who underwent biopsy.

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**FINANCIAL DISCLOSURE:** None

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