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Renal biopsies in patients with HIV and kidney disease and its clinical correlation

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Abstract:
Background*: Acquired Immunodeficiency Syndrome(AIDS) is caused by Human Immunodeficiency Virus) which effects the human immune system. Renal involvement is seen in 5-30% of patients with HIV. Worldwide, in HIV patients, chronic kidney disease has become an epidemic especially in Black population. Renal biopsy is an essential tool to know the histopathology of kidney disease in patients with HIV. HIV associated nephropathy(HIVAN) is a glomerular disease seen in HIV patients. As per Western and African studies, HIVAN constitutes 60% of renal biopsies in HIV patients.*
Aims and Objectives*: To study the clinical profile and renal histopathology in HIV patients presenting with kidney disease . Objective is to study the spectrum of renal disorders in HIV patients. To study the biochemical and other laboratory abnormalities and the need for renal biopsy in these patients.*
Materials and methods*: All HIV patients ,above the age of 18yrs presenting with kidney disease admitted in nephrology wards of Andhra Medical College ,King George Hospital, Visakhapatnam, Andhra Pradesh, India between April, 2019 to December, 2020 were included in the study.*
Results*: Out of the total 30 patients, 18 are males and 12 are females. Most patients belong to 30 to 39 years age group. Most common symtom is oliguria. Comorbid illnesses are hypertension in ten patients and diabetes in three patients. Most common renal histology is infection related glomerulonephritis.*
Conclusion: *Out of the thirty patients who are studied, the most common renal histologies are infection related glomerulonephritis and focal segmental glomerulosclerosis. HIVAN is not seen in our study. Low CD4 counts are associated with pyelonephrits.*
Key Words*: Focal segmental glomerulosclerosis,Tubulointerstitial, HIV associated nephropathy*

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I. Introduction

Acquired immunodeficiency syndrome(AIDS) is caused by human immunodeficiency virus(HIV), which involves the human immune system. Worldwide, in the HIV population, renal disease is seen as a common complication, and prevalence is about 5-30 %1,2 . Worldwide, in HIV patients chronic kidney disease has become epidemic, especially among the Black population.1 Renal pathology is divided into glomerular, tubulointerstitial, and vascular diseases.

HIV-associated nephropathy(HIVAN) is a glomerular disease directly related to HIV infection, which is well established in North America, Africa, and Western Europe especially among the black population. In HIV patients around 60 % of renal biopsies show HIVAN in Western and African studies. HIVAN is a collapsing variant of focal glomerulosclerosis (FSGS) associated with microcystic dilatation in tubules and tubulointerstitial injury. It usually presents with rapidly progressing renal failure and proteinuria, It is associated with high mortality . Due to the introduction of ART for all HIV patients, the incidence of HIVAN has decreased and the incidence of non- HIV- associated chronic kidney diseases (CKD) has increased . Because of the high burden of kidney diseases in HIV- infected patients, the Infectious Diseases Society of America (IDSA) recommends screening for kidney disease using urinalysis and estimation of renal function . These guidelines further recommend proteinuria assessment using quantitative methods to allow earlier identification of kidney disease. Renal biopsy is advocated wherever feasible, because the treatment options and prognosis are influenced by the actual histological diagnosis. While HIVAN has been reported consistently in Western studies, the prevalence in studies from Asia has been found to low/absent. The available studies from India differ strikingly, with some studies showing presence of HIVAN, whereas others reporting complete absence of this entity .

With this perspective, the present study was carried out to elucidate the histological spectrum of renal disease in HIV patients from a tertiary care center from India. Kidney biopsies are performed in HIV patients with proteinuria ≥1 g/day, to delineate the glomerular lesions including presence of possible HIVAN.

II. Aim

To study the clinical profile and renal histopathology in HIV patients on ART and presenting with kidney disease

III. Objectives

1. To study the spectrum of kidney diseases in HIV patients
2. To study the biochemical and other laboratory abnormalities and the need for renal biopsy in these patients

IV. Materials And Methods

The present study was conducted among HIV patients who presented with renal disorder, were older than 18 years, admitted to the Department of Nephrology, Andhra Medical College, King George Hospital, Visakhapatnam, during the period of April 2019 to December 2020.

Methodology:

• **Study design**: Cross-sectional study
• **Study setting**: Inpatient ward; Department of Nephrology, King George Hospital, Visakhapatnam.
• **Duration of study**: April 2019 to December 2020.
• **Sample size**: All patients who fulfilled the inclusion criteria and willing to give consent are enrolled in the study.
• **Consent**: Written informed consent is taken from each patient enrolled in the study.

Inclusion criteria: • Age above 18 yrs. • HIV/AIDS patients with renal disorder.

Exclusion criteria • Age below 18 yrs. • Known or newly diagnosed CKD. • Pregnancy. • Patients who were not willing to give consent for the study.

Method of data collection: Renal disorder was diagnosed by taking detailed clinical history and performing renal function tests. Patients were evaluated with baseline haematology and biochemistry. Duration of anti retroviral drugs is taken. Associated co-morbidities, interventions, treatment, progress and any significant event during the stay at the hospital . Urine examination, 24-hour urine protein, ANA, ANCA, C3, C4 are done. CD4 lymphocyte count is done for all patients at presentation. Ultrasound abdomen will be done. Renal biopsy is done in all patients with no contraindications, and biopsy subjected to light microscopy and immunofluorescence

V. Statistical Analysis

Data is entered into Microsoft excel spreadsheet version 2013. Later exported to SPSS (statistical package for social science) version 17. Analysis is done in both Microsoft excel spreadsheet version 2013 and SPSS. Quantitative variables are described in the form of mean and standard deviation. Qualitative variables are described in the form of frequency and percentages. Tests of significance used are the independent sample ttest and Fisher's exact test. Odds ratio is used to estimate the strength of association. A p value of 0.05 or less is considered significant.

VI. Results

From APRIL 2019 to DECEMBER 2020 a total of 30 patients with HIV/AIDS patients who presented with renal disorder were included in the study and renal biopsies were done.

Gender distribution

Male patients comprise of 60 %(n=18) of the study population, while female patients were 40%(n=12). Males were more common than females with ratio of male: female 1.5:1.

Table 1

	Frequency	**Percent**
Female	12	40.0
Male	18	60.0
Total	30	100.0

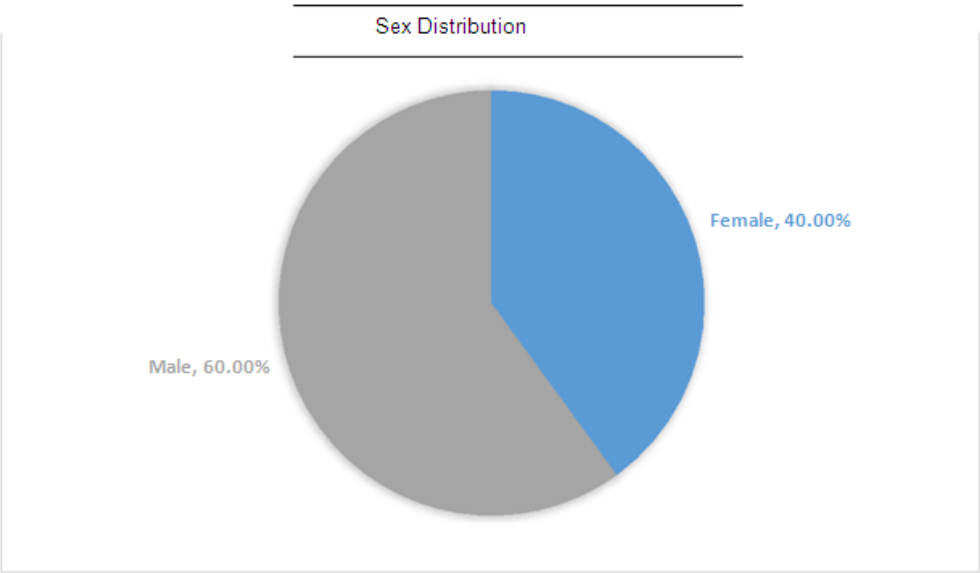


Figure 1

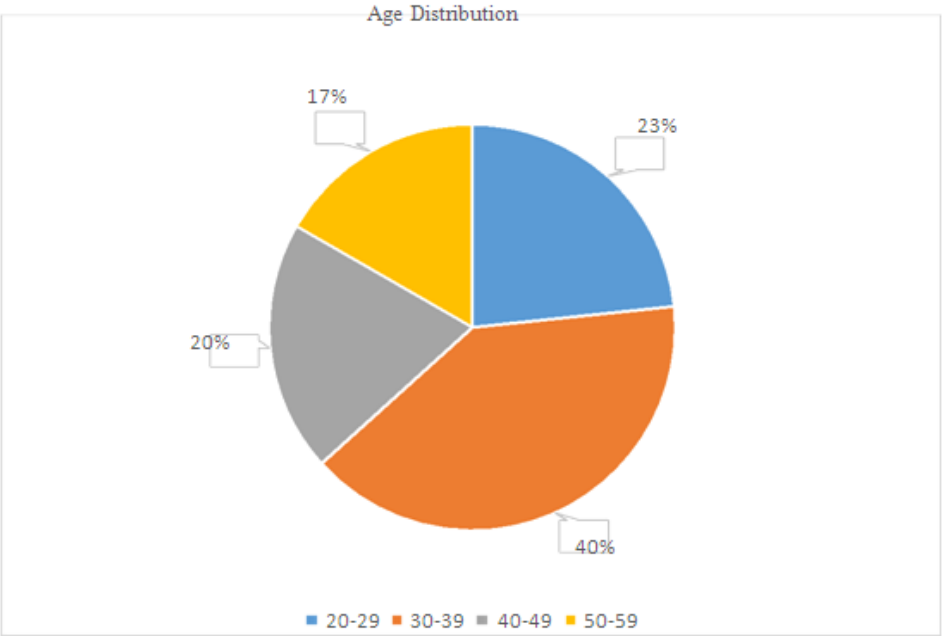
Age Distribution

Most of the patients belong to 30-39 age group (n=12).Followed by 7 patients in 20-29 age group .6 patients in 40-49 age group and 5 patients in 50-59 age group.

Table 2

Age	**Male**	**Female**	**Frequency**	**Percentage**
20-29	4	3	7	23.3%
30-39	8	4	12	40%
40-49	5	1	6	20%
50-59	1	4	5	16.7%
Total	18	12	30	100%

Figure 2



Mean age of the patients is 39.27 years with standard deviation of 9.247 years.

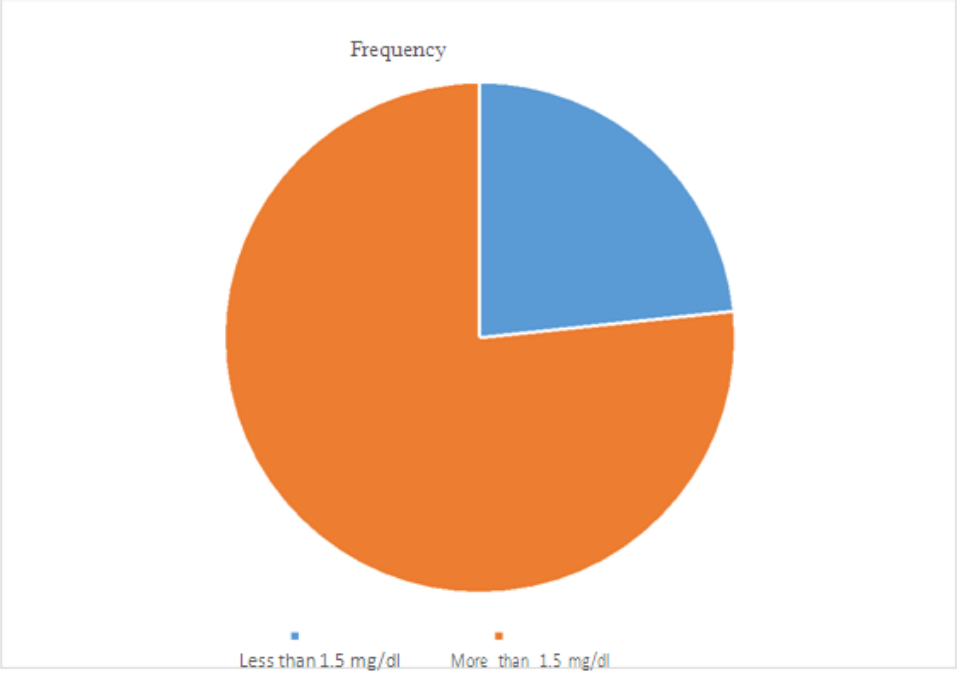
COMPARISION OF RENAL FUNCTION WITH HISTOLOGY PATTERN

In our study 23 patients showed elevation of serum creatinine more than 1.5 mg/dl out of which four patients showed infection related glomerulonephritis.seven patients had serum creatinine less than 1.5 mg/dl out of which two patients showed membranous nephropathy.

Table 10

Serum Creatinine	**Frequency**	**Most Common Histology**	**Number of patients**
Less than 1.5 mg/dl	**7**	**Membranous nephropathy**	**2**
More than 1.5 mg/dl	**23**	**Infection related glomerulonephritis**	**4**

Figure 8



RENAL BIOPSY

LIGHT MICROSCOPY

` Most common diagnosis on renal biopsy is Infection related glomerulonephritis(IRGN) seen in 5 patients(16.67%). Second most common is Focal segmental glomerulosclerosis not specified otherwise (FSGS-NOS) seen in 4 patients (13.3%). Acute pyelonephritis, chronic interstitial nephritis and diabetic nephropathy seen in 3 cases each. Diffuse proliferative glomerulonephritis thrombotic microangiopathy and membranous nephropathy is seen in 2 cases. Acute tubular necrosis, acute interstitial nephritis and endocapillary proliferation is seen in 1 case each.

Table 11

	Frequency	**Percent**
Acute Interstitial Nephritis	1	3.3
Acute Pyelonephritis	3	10.0
Acute tubular necrosis	1	3.3
Chronic Tubulointerstitial Nephritis	3	10.0
Diffuse Proliferative glomerulonephritis	2	6.7
Diabetic Nephropathy	3	10.0
Endocapillary Proliferation with Segmental Sclerosis & focal crescents	1	3.3
Focal Segmental Glomerulosclerosis, not otherwise specified	4	13.3

Infection related glomerulonephritis	5	16.6
Membranous Nephropathy	2	6.7
Mesangio Proliferative glomerulonephritis	3	10.0
Thrombotic Micro Angiopathy	2	6.6
Total	30	100.0

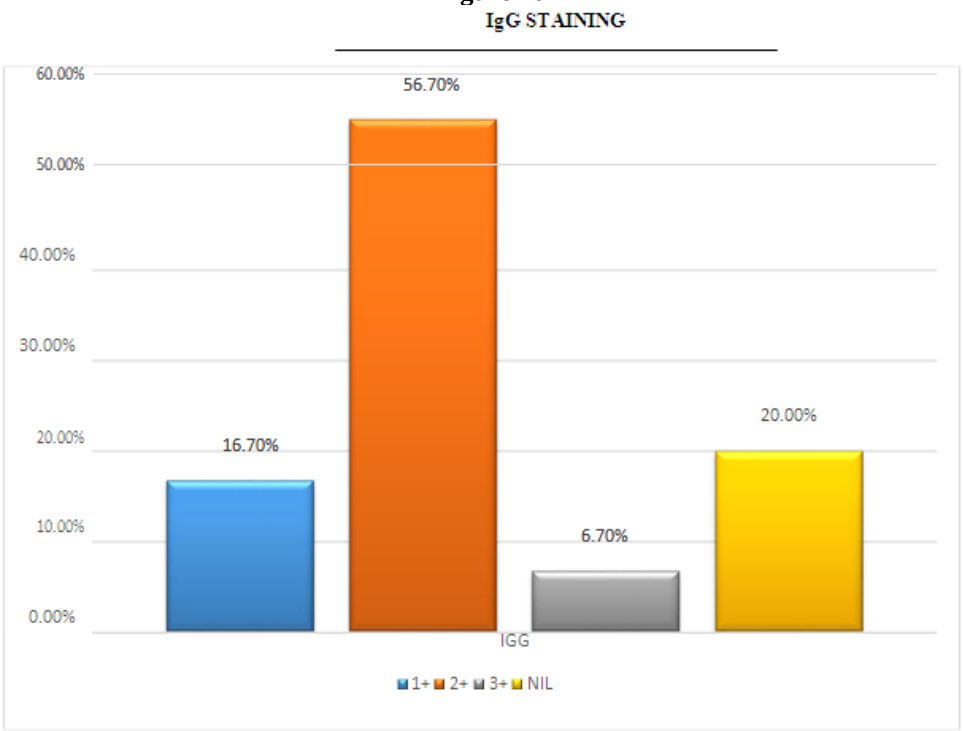
Figure 9

IgG:
In our study IgG positivity of 1+ is seen in 5 patients and 2+ is seen in 17 patients and 3+positivity is seen in 2 patients.

Table 12

	Frequency	Percent
1+	5	16.7
2+	17	56.7
3+	2	6.7
Nil	6	20.0
Total	30	100.0

Figure 10

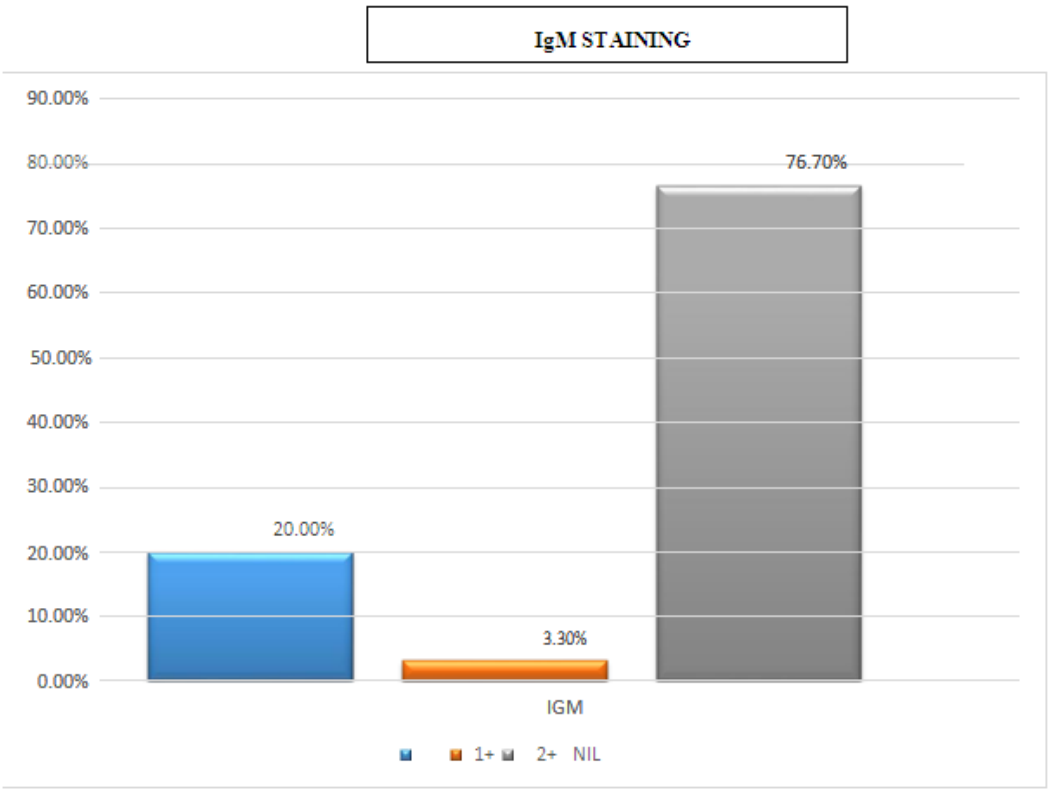


IgM:
In our study IgM positivity of 1+ is seen in 6 patients and 2+ positivity is seen in 1 patient.

Table 13

	Frequency	Percent
1+	6	20.0
2+	1	3.3
Nil	23	76.7
Total	30	100.0

Figure 11



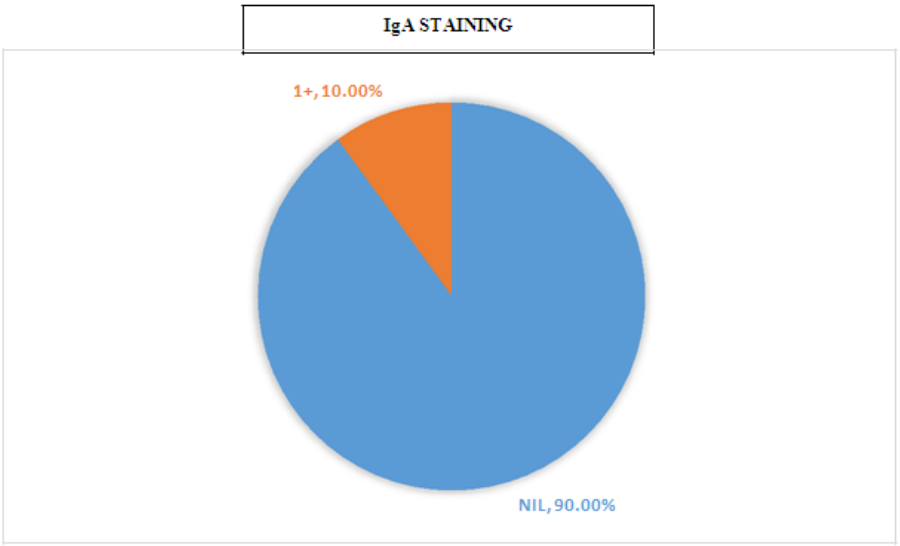
IgA:

In our study IgA positivity is seen in 3 patients.

Table 14

	Frequency	Percent
1+	3	10.0
Nil	27	90.0
Total	30	100.0

Figure 12

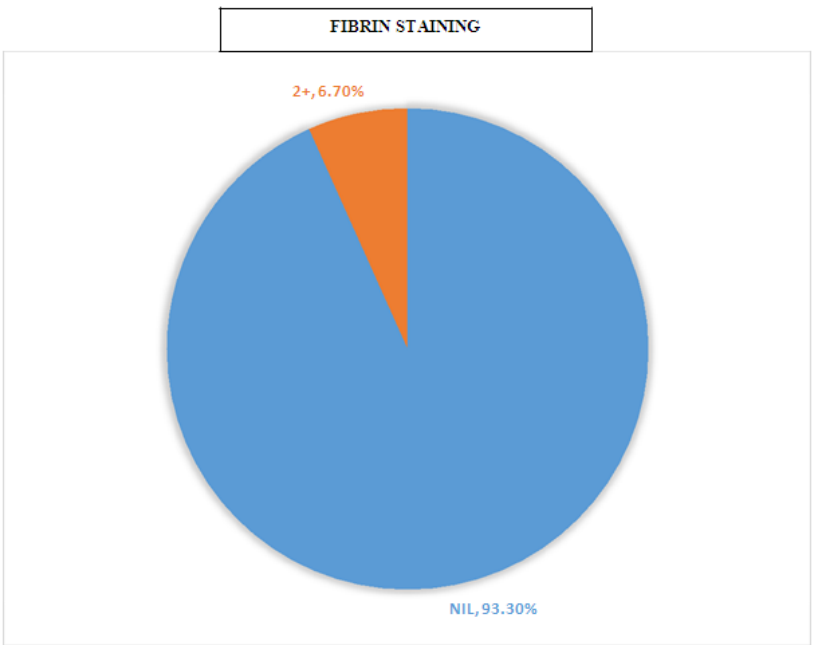


Fibrin:
Immunofluorescence showing fibrin positivity is seen in 2 patients who had thrombotic microangiopathy.

Table 15

	Frequency	Percent
2+	2	6.7
Nil	28	93.3
Total	30	100.0

Figure 13

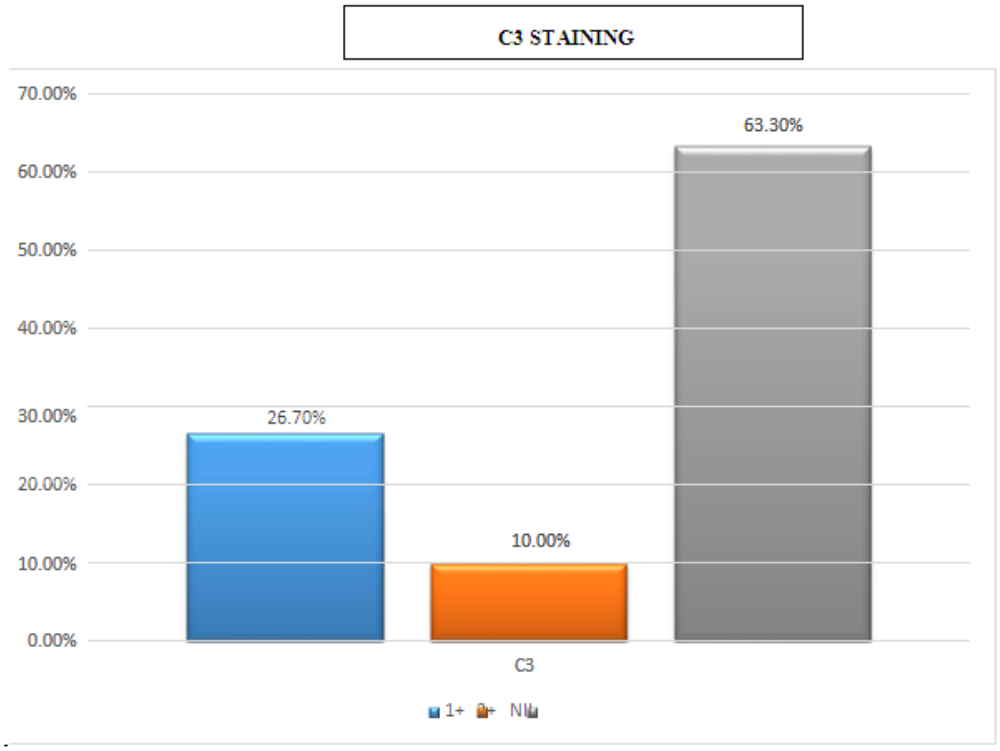


C3 staining:
In our study C3 positivity of 1+ is seen in 8 patients and 2+ positivity is seen in 3 patients.

Table 16

	Frequency	Percent
1+	8	26.7
2+	3	10.0
Nil	19	63.3
Total	30	100.0

Figure 14



GLOMERULAR PATHOLOGY

In our study endocapillary proliferation is seen in 6 patients (30%),focal segmental glomerulosclerosis is seen in 4(20 %),whereas diabetic glomerulosclerosis and mesangioproliferative glomerulonephritis is seen in 3 patients (15%) and membranous nephropathy and thrombotic microangiopathy is seen in 2 patients.

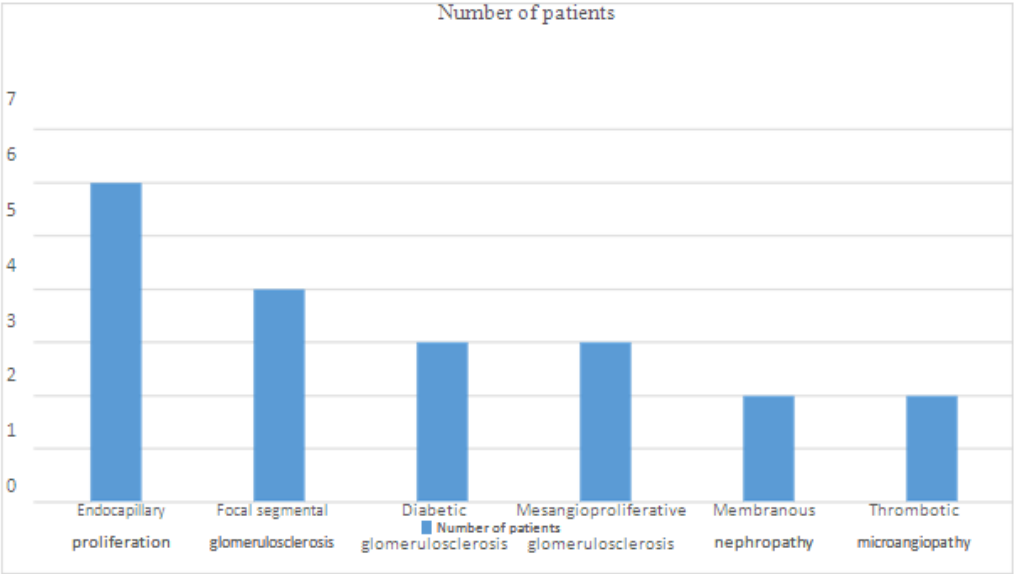
In our study 18 patients were male and 12 patients were female and male: female ratio is 3:2 which is similar to other studies from India and a study from brazil from Cavalcante.

Table 17

Glomerular pathology	Number of patients	Percentage
Endocapillary proliferation	6	30%

Focal segmental glomerulosclerosis	4	20%
Diabetic glomerulosclerosis	3	15%
Mesangioproliferative glomerulosclerosis	3	15%
Membranous nephropathy	2	10%
Thrombotic microangiopathy	2	10%

Figure 15



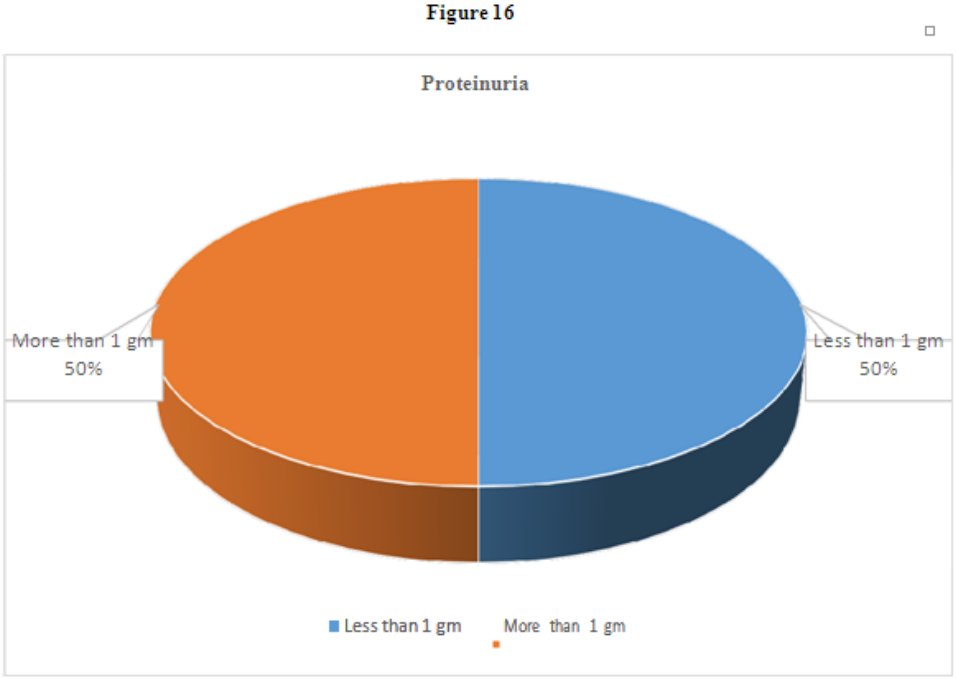
COMPARISION OF PROTEINURIA WITH HISTOLOGY PATTERN

In our study 15 patients showed elevation of proteinuria more than 1 gm out of which 3 showed acute pyelonephritis and in remaining 15 patients had proteinuria more than 1 gm out of which 4 showed focal segmental glomerulosclerosis.

Table 18

24 hr urine protein	Frequency	Most Common Histology	Number of patients
Less than 1 gm	15	Acute pyelonephritis	3
More than 1 gm	15	Focal segmental glomerulosclerosis	4

Figure 16



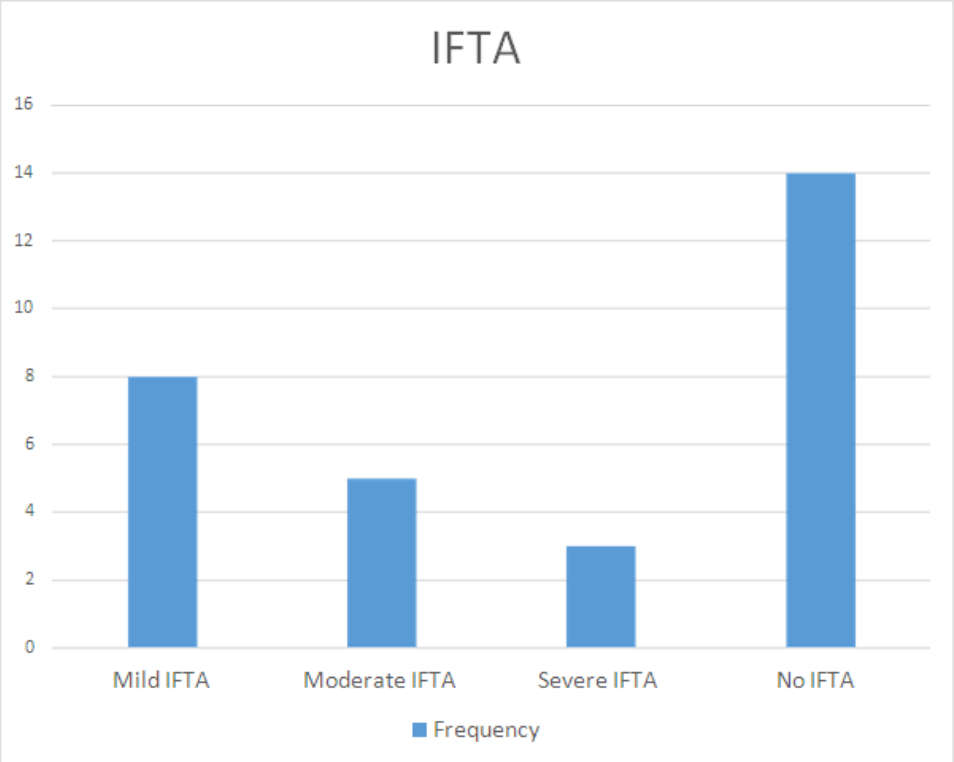
IFTA

In our study intersititium is not involved in 14 patients(46.66%),mild IFTA (0-25%)is seen in 8 patients(26.67%).Moderate IFTA(25-50%) is seen in 5 patients (16.67%) and severe IFTA (more than 50%) seen in 3 patients(10%).

Table 20

Interstitial fibrosis and Tubular atrophy (IFTA) in LM	Frequency	Percentage
Mild IFTA	8	26.67%
Moderate IFTA	5	16.67%
Severe IFTA	3	10%
No IFTA	14	46.66%
Total	30	100%

Figure 17



VASCULAR LESIONS ON BIOPSY

In our study vascular involvement is seen in 6 patients (20%),out of which 3 showed intimal hyperplasia , 2 showed hyaline arteriosclerosis and 1 showed medial hypertrophy.

Table 21

Vascular lesions on biopsy	**Frequency**	**Percentage**
Normal	24	80%
Intimal hyperplasia	3	10%
Medial hypertrophy	1	3.33%
Vascular necrosis	0	0%
Hyaline arteriosclerosis	2	6.66%

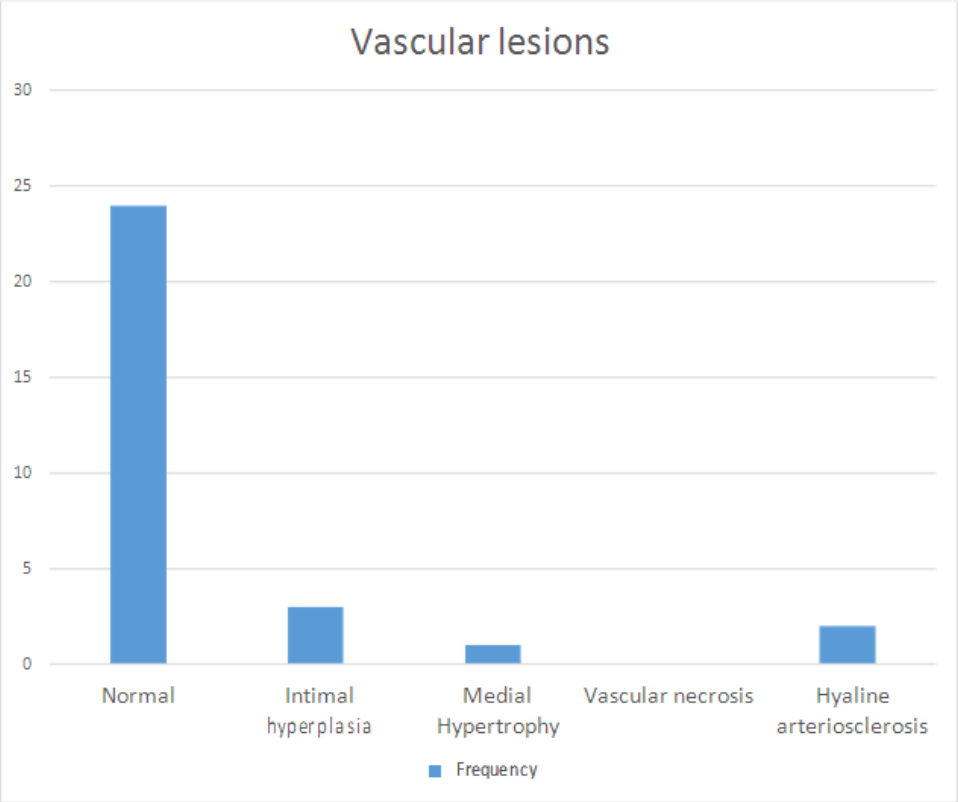


Figure 18

VII. Discussion

A total of 30 HIV/AIDS patients presenting with renal disorder to the department of nephrology from April 2019 to December 2020 were identified and underwent renal biopsy. 30 patients were enrolled into the study and evaluated.

Mean age of patients at presentation in our study was 39.27±9.247 years which is higher compared to Indian studies i.e., Gupta et al143 and Prakash et al144. Age group of 30-39 age group were most involved with 8 patients.

Table 22

Study Group	**Mean Age(years)**	**Standard Deviation**
Our study	39.27	9.247
Gupta et al	33.9	7.9
Prakash et al	35.7	9.76

In our study 18 patients were male and 12 patients were female and male: female ratio is 3:2 which is similar to other studies from India and a study from brazil from Cavalcante.

In our study most common symptom is oedema which is seen in 16 patients 53.3% patients which is high compared to study by Prakash et al from north India who reported oedema in 24 % of patients. This is in contrast to study by Gupta et al who noted fever as most common symptom. In our study oliguria is second most symptom seen in 40% of patients.

Hypertension is common comorbidity seen in 10 patients. Diabetes is seen in only 3 patients. Mean random blood sugar of study population is 117.9 mg/dl and standard deviation is 46.94/dl. Mean serum calcium of study population is 8.33 mg/dl and standard deviation is 0.66 mg/dl. Mean phosphorus of study population is 3.85 mg/dl and standard deviation is 0.91 mg/dl. Mean uric acid of study population is 5.77 mg/dl and standard deviation is 0.98 mg/dl. Mean albumin of study population is 2.867 gm/dl and standard deviation is 0.75 gm/dl. Mean serum cholesterol of study population is 189.9 mg/dl and standard deviation is 23.3 mg/dl.

In our study mean CD4 lymphocyte count is 319±191 cells/µl which is higher compared to other Indian studies by Prakash et al and Vijay Gupta et al. which showed mean CD4 cell count of 201±151 and 221±151, respectively.

Table 23

Study	**Mean CD4 count**	**Standard deviation**
Our study	319	191
Prakash et al	201	151
Gupta et al	221	251

In patients with CD4 lymphocyte count less than 200 infection related glomerulonephritis and acute pyelonephritis is most common finding and in CD4 count more than 200 focal segmental glomerulosclerosis is the most common finding which is in par compared to north India studies.

Mean creatinine at presentation in our study population is 2.5±1.2 mg/dl which is lower compared to other studies from North India. Among 30 patients included in the study, 3 patients has no proteinuria on urine dipstick examination and rest of 27 patients has a minimum of 1+ proteinuria while 3+ protein on urine dipstick is seen in 9 patients.

Mean 24-hour urine protein is 1.5 ±1.49 grams/day. Proteinuria of more than 1 gram per day is seen in 15 patients (50%) which is higher compared to other Indian studies by Bhupender et al. and Prakash et al.

Renal biopsy was done in all patients in view of either elevated serum creatinine or significant proteinuria. Most common histopathological finding in light microscopy is Infection related glomerulonephritis found in 5 patients (16.66%) which is in contrast to other studies, where it is rare. In contrast to our study no case of IRGN is seen in either Indian or major biopsy series from United States. Thus infection related glomerulonephritis is an inconsistent finding in our study. However thrombotic microangiopathy is seen in 2 patients which is also seen in 2 patients in a study by Gupta et al.

Table 24

Study	**Most common histolopathological lesion**	**Percentage**
Our study	Infection related glomerulonephritis	5(16.66%)
Prakash et al	Mesongioprolifertive glomerulonephritis	5(35.7%)
Gupta et al	Mesongioprolifertive glomerulonephritis	9(35.6%)
Varma et al [145]	Mesongioprolifertive glomerulonephritis	8(32%)
Satish et al[146]	Diabetic nephropathy	7(23.3%)

Focal segmental glomerulosclerosis was found in 4 patients (13.33%) especially in patients with proteinuria of more than 1 gm/day.

HIVAN has been reported in studies from US, Western Europe as a most common glomerular lesion in HIV seropositive patients. Classic HIVAN can be seen at any stage of HIV infection but most commonly seen in advanced disease. HIVAN is reported in lesser frequency in Hispanic population and variable in Asian Indian population. Prevalence of HIVAN in studies from outside India have reported from 0 to 83%. The current trend of HIVAN is declining as a result of widespread use of ART. We have not observed any case of HIVAN in HIV patients in our current study. Varma et al and Prakash et al also did not find any case of HIVAN in their studies.

Our study showed mesangioprolifertive glomerulonephritis in 3 (10%) of patients. While it was the most common glomerular lesion in a study by Prakash et al. (37.5%). This is in contrast from western world were mesangioproliferative glomerulonephritis is infrequent. No case of mesangioproliferative glomerulonephritis is seen in major biopsy series from United States but found in 15% patients from Italy.

Isolated chronic tubulointerstial nephritis was the predominant non-glomerular lesion in our study (10%). This is low when compared to Prakash et al. (15.38%) and Verma et al. (20%). Unlike infection related glomerulonephritis, incidence of tubulointerstial nephritis has been consistently reported low in Indian studies as compared to a study from Paris by Nochy et al[147] which showed tubulointerstitial nephritis in 48% and 52% patients of Blacks and Caucasians respectively.

Table 25

Study	Chronic interstial nephritis patients	Percentage involved
Our Study	3	10%
Prakash et al	2	15.38%
Verma et al	5	20%
Nochy etal	30	50%

Epidemiological data showing a decline in the incidence of HIVAN and HIV-associated ESRD in the United States after introduction of cART, suggest that effective control of viral replication can prevent the development of HIVAN. A study of 221 HIV-positive patients in South Africa reported that HIVAN showed response to ART. HIV-associated thrombotic microangiopathy also appears to benefit from ART, and a decline in incidence has been reported with widespread ART use. Thus, combined ART has changed the epidemiology of HIV-related kidney diseases. HIVICK and noncollapsing form of FSGS are increasingly reported in the post ART era. HIVICK is less likely than HIVAN to progress to ESRD and thought to be associated with greater exposure to ART and hepatitis C coinfection. Over the past two decades, a decreasing frequency of classic HIVAN has been observed in African patients living in Europe. ART has been associated with lower incidence of HIVAN, improved kidney function, and lower risk of ESRD in observational studies of patients with biopsy-confirmed or clinically suspected HIVAN. These data reveal that ART seems to have a beneficial role in the prevention and treatment of HIVAN.

VIII. Conclusions

Thirty patients presented to King George Hospital, Visakhapatnam, who are HIV-positive and diagnosed with renal disorder were studied. The major cause of renal disorder in our study was infection related glomerulonephritis and focal segmental glomerulosclerosis is second most common pathology. HIVAN was not identified in our study which is consistent with other north Indian studies. Low CD4 count was associated with infections related renal disorder and pyelonephritis. HIVICK is seen increasingly in HIV patients due to widespread use of ART and by avoiding nephrotoxic drugs. Chronic interstitial nephritis is increasing in patients of HIV due to widespread use of antibiotics and other drugs. Diabetic nephropathy is seen in HIV patients due to longevity of survival of HIV patients due to ART drugs and control of opportunistic infections.

Early recognition and biopsy can lead prompt recognition of underlying renal disorder in patients with HIV sero-positivity. This in turn results in early institution of treatment, and can prevent or slow progression of renal disorder to ESRD.

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