

## A CLINICOPATHOLOGICAL STUDY OF ACUTE KIDNEY INJURY FROM A TERTIARY CARE CENTRE

NEERAJ DHAMEJA<sup>a1</sup>, MAYURAKSHI DAS<sup>b</sup>, A. P. NARRENDRAN<sup>c</sup> AND ARVIND GUPTA<sup>d</sup>

<sup>ab</sup>Department of Pathology, Institute of Medical Sciences, BHU, Varanasi, Uttar Pradesh, India

<sup>c</sup>Department of Pathology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

<sup>d</sup>Department of Medicine, Motilal Nehru Medical College, Allahabad, Uttar Pradesh, India

### ABSTRACT

Acute kidney injury (AKI) is characterized by abrupt rise in serum creatinine and decreased urine output over a course of hours to days. The causes may be pre-renal, renal or post-renal. Pre-renal and post-renal causes often don't warrant renal biopsy in clinical practice. For diagnosis of renal causes of AKI or those refractory to treatment, renal biopsy is performed and in such cases helps in effective management and predicting prognosis. The aim of this study was to determine the morphological features of AKI in our setup and to know the incidence of different causes. Histopathological evaluation of renal biopsies performed with AKI as indication between December 2007 and June 2010 were selected for this study. The underlying clinical conditions were grouped into infections (septicaemia, malaria, Hepatitis B), post-transplant changes, collagen vascular diseases (ANCA positive), underlying renal diseases (diabetes mellitus, hypertension), nephrotoxic drugs intake, multiple myeloma and postpartum. The histopathological spectrum of AKI included acute tubular necrosis with acute interstitial nephritis, crescentic glomerulonephritis, acute cortical necrosis, acute interstitial nephritis, cast nephropathy, diffuse proliferative glomerulonephritis, malignant nephrosclerosis leading to haemolytic uremic syndrome, pyelonephritis, collapsing glomerulopathy, diffuse global glomerulosclerosis, and focal proliferative glomerulonephritis with necrosis and crescent formation. Our study of 84 cases carried out in a tertiary healthcare centre in North India proves that renal biopsy can be an adjuvant diagnostic modality in identifying the underlying renal lesions and aiding the diagnosis and treatment of AKI.

**KEYWORDS:** Acute Kidney Injury, Acute Tubular Necrosis, Acute Interstitial Nephritis, Crescentic Glomerulonephritis, Thrombotic Microangiopathy, Acute Cortical Necrosis

Acute kidney injury (AKI) is currently defined by the Kidney Diseases: Improving Global Outcomes (KDIGO) clinical practice guidelines workgroup as a rise of serum creatinine at least 0.3mg/dl from baseline within 48 hours or at least 50% higher from baseline within one week or a reduction in urine output to less than 0.5ml/kg per hour for longer than 6 hours (KDIGO, 2012). Causes of AKI can be categorized into pre-renal, renal and post-renal. The pre-renal causes include factors which lead to reduced renal blood flow, commonly hypovolemia and decreased effective circulatory volume due to congestive cardiac failure. Post-renal causes include obstruction of the urinary tract. AKI can also be superimposed on underlying kidney diseases which involve glomeruli, tubules, interstitium or blood vessels. Sepsis is a common cause of AKI in developing countries as is drug-induced AKI (Lameire, 2013). Acute kidney injury is usually diagnosed based on clinical history, blood investigations and urinary findings. Kidney biopsy is done when pre-renal and post renal causes have been excluded and intrinsic causes of AKI are suspected.

The objective of this study was to determine the histopathological features in patients presenting with acute kidney injury. For purpose of this study, those cases with sudden onset oliguria/anuria and rise in

serum creatinine levels were considered as having acute kidney injury.

### MATERIALS AND METHODS

We reviewed the clinical case files and pathology reporting registers of a tertiary health care center in Varanasi to identify the renal biopsy specimens processed and reported from December 2007 to June 2010.

A total of 165 renal biopsies were processed during this period. All clinical information pertaining to each renal biopsy was reviewed which included the clinical history, physical examination, laboratory findings and indication for each biopsy. Acute kidney injury was considered the indication for biopsy if the patients presented with complaints of sudden onset oliguria and raised serum creatinine or there was mention of acute renal failure on the requisition form. Based on these findings, 84 cases were found to have AKI and the following relevant information was recorded wherever present such as age, sex, serum creatinine level, presence or absence of proteinuria, hematuria (gross/microscopic), presence or absence of long standing comorbidities such as diabetes mellitus and hypertension, drug history, history of any underlying infection, malignancy, obstetrical history,

history of recent surgical procedures, positivity for autoantibodies like anti-nuclear antibody (ANA ) and anti-neutrophilic cytoplasmic antibody (ANCA) and any pre-biopsy specific diagnosis provided by the clinician.

The salient morphological features of these 84 renal biopsy specimens were studied by light microscopy and searched for glomerular, tubular, interstitial and vascular lesions. Immunofluorescence and electron microscopy could not be done due to non-availability.

**RESULTS**

This study constituted 84 renal biopsies without inclusion of any repeat biopsies from same patient. 78 adults and 6 children of which 65 were males and 19 were females were included in this study. Among children, the most commonly affected age group was 11-15 years and among adults, it was 50-70 years. (Figure 1)

Contributing factors to the development of AKI encompassed a wide spectrum. 20 patients had septicemia, one patient had Plasmodium falciparum infection while another had Hepatitis B virus infection. 18 patients had underlying renal disease with diabetes mellitus and hypertension being the most common comorbidities. Among other causes of AKI, three patients had developed post-partum AKI, three had malignant hypertension, two had anti neutrophil cytoplasmic antibody (ANCA) positivity and one developed AKI post-renal transplant.

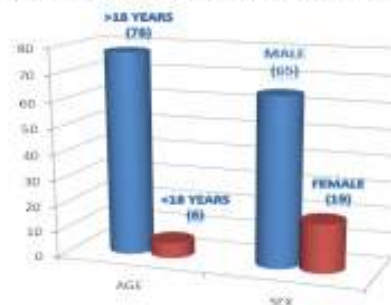
On histopathological examination, acute tubular necrosis and acute interstitial nephritis were the most common causes of AKI in this study comprising 25 cases each (Figures 2-3). The cause of acute interstitial nephritis was suspected to be drug-induced; however, exact drug history could not be elicited in many patients. Many of the patients with acute tubular necrosis had septicemia. Among the glomerular diseases, crescentic glomerulonephritis was the most common accounting for 13 cases (Figure 4). Diffuse proliferative glomerulonephritis comprised of 3 cases (Figure 5). Acute cortical necrosis was seen in four patients; three of which were in young post-partum females (Figure 6). One child with post diarrheal hemolytic uremic syndrome and three elderly male patients with malignant hypertension had thrombotic microangiopathy (Figures 7-8). Diffuse global glomerulosclerosis and pyelonephritis comprised four and two cases respectively (Figures 9-10). Cast nephropathy due to myeloma (Figure 11), collapsing

glomerulopathy in a human immunodeficiency virus seronegative young male patient with sudden deterioration of renal function (Figure 12), vascular change (Figure 13) and focal proliferative glomerulonephritis with necrosis (Figure 14) comprised of one case each. The patient with vascular change (intimal proliferation of the blood vessels with myxoid change) was a case of collagen vascular disease and showed anti-nuclear antibody positivity. (Figure 15, Table 1)

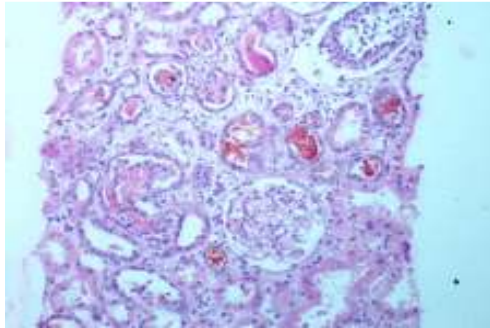
**Table 1: Histomorphological Spectrum of Acute Kidney Injury**

Morphology of AKI	%	Number of Cases
Acute Tubular Necrosis	30%	25
Acute Interstitial Nephritis	30%	25
Crescentic Glomerulonephritis	15%	13
Acute Cortical Necrosis	5%	4
Cast Nephropathy	1%	1
Diffuse Proliferative Glomerulonephritis	4%	3
Vascular Change	1%	1
Pyelonephritis	2%	2
Hemolytic Uremic Syndrome-Thrombotic Microangiopathy	5%	4
Collapsing Glomerulopathy	1%	1
Diffuse Global Glomerulosclerosis	5%	4
Focal proliferative Glomerulonephritis with Necrosis and Crescent	1%	1

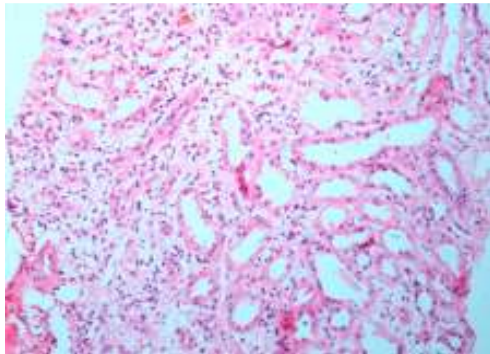
**FIG 1: AGE AND SEX DISTRIBUTION OF AKI CASES**



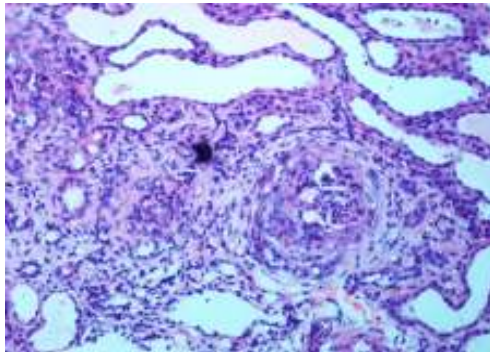
**Figure 1: Age and sex distribution of AKI cases**



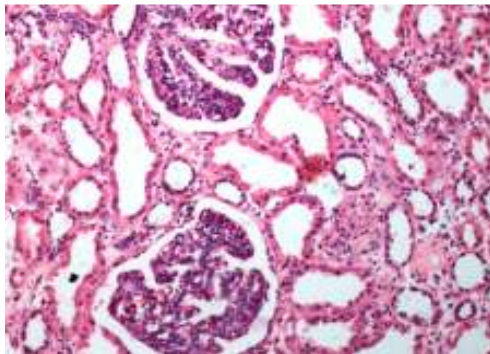
**Figure 2: Acute Tubular Necrosis with Flattened Tubular Epithelium and Red Blood Cell Casts (H&E, 20x)**



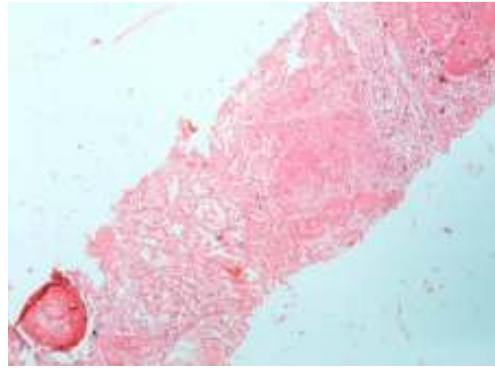
**Figure 3: Acute Interstitial Nephritis with eosinophils in the interstitium (H&E, 20X)**



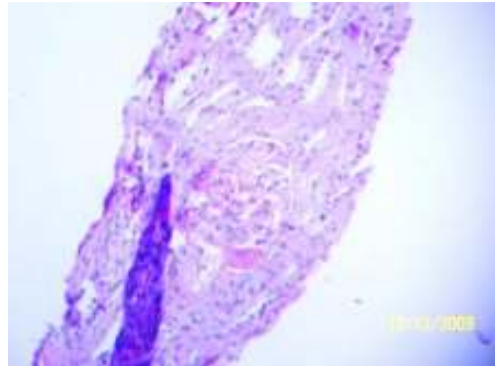
**Figure 4: Crescentic Glomerulonephritis (H&E, 20X)**



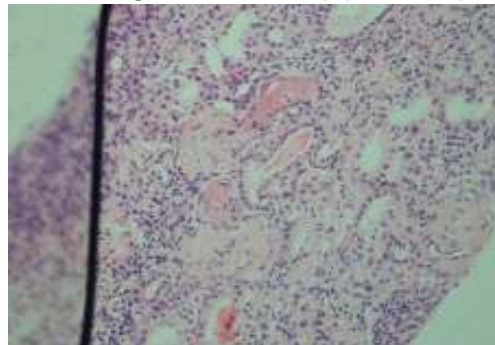
**Figure 5: Post infectious diffuse proliferative GN (H&E, 20X)**



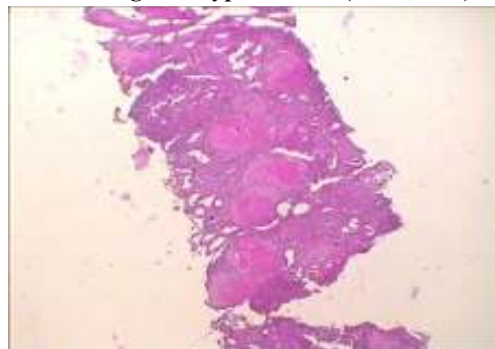
**Figure 6: Acute cortical necrosis (H&E, 10X)**



**Figure 7: Thrombotic Microangiopathy in a child with Hemolytic Uremic Syndrome (subendothelial thickening with thrombosis) (H&E, 20X)**



**Figure 8: Thrombotic Microangiopathy in an adult with malignant hypertension (H&E, 20X)**



**Figure 9: Diffuse Global Glomerulosclerosis (Periodic acid Schiff, 10X)**

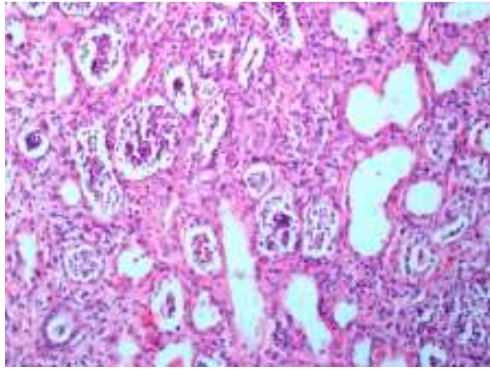


Figure 10: Pyelonephritis (H&E, 20X)

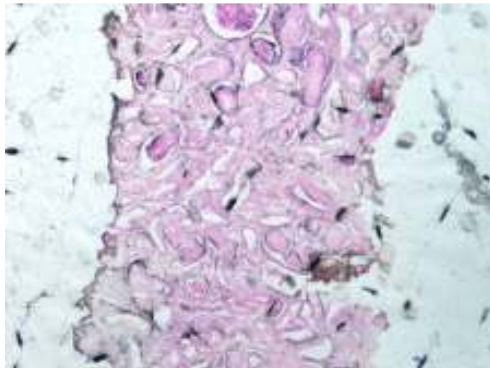


Figure 11: Cast nephropathy (Periodic acid Schiff, 20X)

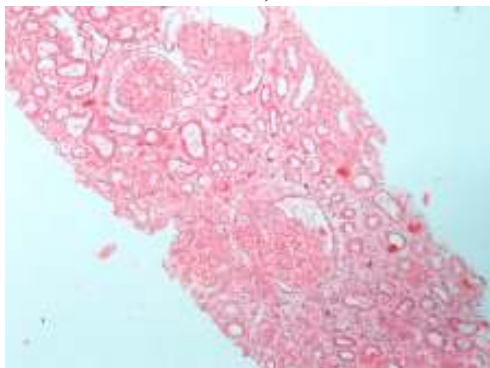


Figure 12: Collapsing Glomerulopathy (H&E, 10X)

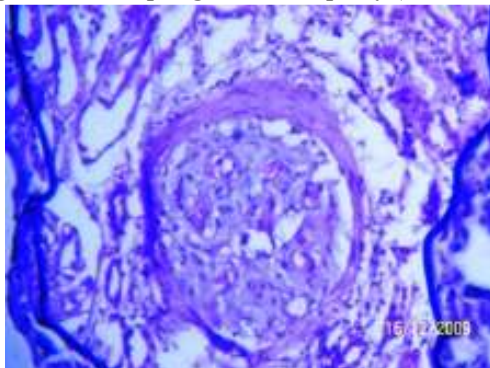


Figure 13: Vascular myxoid change (H&E, 20X)

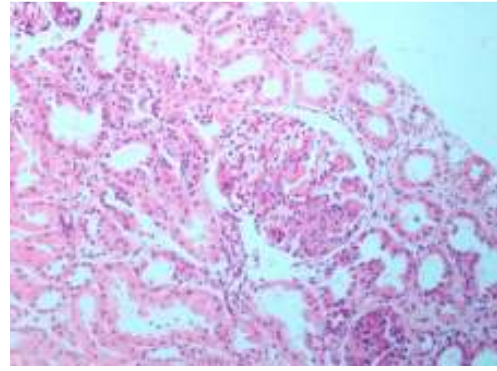


Figure 14: Focal Proliferative Glomerulonephritis with necrosis (H&E, 20X)

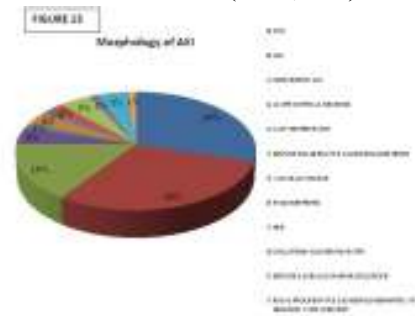


Figure 15: Graphical representation of AKI causes

#### DISCUSSION

Acute kidney injury (AKI) is sudden deterioration in renal function characterized by rise in serum creatinine and reduced renal output; a complex disorder with variable causes and varied clinical manifestations ranging from raised serum creatinine to anuric renal failure. The prognosis of patients with intrinsic acute renal failure is poor with a mortality rate of 40-80% in the intensive care setting (Devarajan, 2006). Study by Laingoset *al*(2006) using National Hospital Discharge Survey found acute renal failure to be associated with adverse outcomes including higher hospital associated mortality and prolonged length of stay in the hospital.

Pre-renal and post-renal causes of AKI can be excluded by clinical history and radiological examination. Due to conflicting views regarding kidney biopsy in AKI, the procedure is less frequently done. Several studies have suggested significant discordance between pre-biopsy and post-biopsy diagnosis in the setting of acute kidney injury and because of reluctance to perform kidney biopsy, treatable causes can be missed and delay in treatment may occur (Stillman, 2008). According to Lameire *et al* (2013) the time and place of renal biopsy depends on the clinical context, but is helpful for exclusion of intrinsic causes of renal

failure and should be undertaken promptly if these disorders are suspected.

Epidemiology of acute kidney injury differs in developed and developing countries. In developed countries, it is due to surgical complications, hypovolemia and drugs. In developing countries, infections play a major role in causing AKI. Different tropical infections like malaria (1-5%), leptospirosis (20-85%), dengue hemorrhagic fever (3.3-10% in adults and 0.9% children) can cause acute kidney injury (Lameire *et al*, 2013). Diarrheal diseases, acute post-infectious glomerulonephritis, human immunodeficiency virus infection, drugs, obstetrical complications are also important causes of acute kidney injury (Lameire *et al*, 2013). In a study from South India, Krishnamurthy *et al* (2013) found infections (55.4%) to be the most common cause followed by acute glomerulonephritis (16.9%), cardiac diseases (4.8%), envenomations (4.2%) and hemolytic uremic syndrome (3.6%). Pneumonia constituted 26.1% of the infections. Tropical febrile illnesses like dengue, scrub typhus, enteric fever, cholera, malaria, tuberculosis and leptospirosis constituted 15.6% of the children with acute kidney injury. Study by Mehta *et al* (2012) found acute tubular necrosis to be the most common cause of AKI in children followed by acute interstitial nephritis and bladder outlet obstruction. Sepsis and shock were the chief predisposing conditions for acute tubular necrosis. Among tubular causes, acute tubular necrosis (ATN) is the most frequent cause of intrinsic acute kidney injury, however, in the absence of a kidney biopsy, it is often a presumptive diagnosis.

Acute tubular necrosis results from prolonged renal ischemia (hypoperfusion after surgery, bleeding, dehydration, shock) or sepsis, drugs and pigment injury from myoglobin and hemoglobin (Lameire *et al*, 2013). Prominent morphologic features of ischemic AKI include loss of proximal tubule brush border, patchy loss of tubule cells, focal areas of proximal tubular dilation and distal tubular casts, and areas of cellular regeneration (Vivette *et al*, 2005). The glomeruli are usually unremarkable.

Glomerular causes include proliferative glomerulonephritis either extra-capillary (crescentic) or intra-capillary. Interstitial causes include interstitial nephritis, mostly due to drugs. The vascular causes include changes in arterioles or small arteries and include fibrinoid necrosis, intimal hyperplasia with myxoid change.

Few studies have evaluated histopathological findings in patients with acute kidney injury. Haas *et*

*al*(2000) evaluated 259 kidney biopsies from patients aged 60 years or more from 1991 to 1998 (total 4264 kidney biopsies were received during this period and 1065 patients were 60 years or above) and found pauci-immune crescentic glomerulonephritis with or without arteritis to be the most common cause of acute renal failure comprising 31.2% of the total cases followed by acute interstitial nephritis comprising 18.6% and acute tubular necrosis with or without nephrotic syndrome comprising 7.5% and 6.7% cases respectively. In a study by Liaño *et al* (1996) on acute renal failure in Spain, acute tubular necrosis was the most common etiology comprising 45% of the cases followed by pre-renal causes (21%), acute on chronic renal failure (12.7%) and obstructive acute renal failure (10%). This was based on clinical features and laboratory investigations. Kidney biopsy was done in only 46 cases of total 748 cases of acute renal failure. Based on histopathological features, crescentic glomerulonephritis was the most common cause of acute renal failure.

In a clinicopathological study of renal biopsies in elderly patients, Uezono *et al* (2006) found 71% patients had ANCA positive crescentic glomerulonephritis and 17% had interstitial nephritis. Histopathological and pre-biopsy clinical diagnosis differed in 15% of patients. López-Gómez *et al* (2008) studied renal biopsy findings in a cohort of patients presenting with acute renal failure in children, adults and elderly patients between 1994 to 2006 and found vasculitis with type 3 crescentic glomerulonephritis to be the most common cause (23.3%) followed by acute interstitial nephritis (11.3%), type 1 and 2 crescentic glomerulonephritis (10.1%) and acute tubular necrosis (5%). Brown *et al* (2012) and Carmo *et al* (2010) studied renal histology in patients presented with acute renal failure or nephrotic syndrome and found crescentic glomerulonephritis and tubulo-interstitial nephritis to be the commonest cause of acute kidney injury.

In the present study, acute tubular necrosis (ATN) and acute interstitial nephritis (AIN) were the commonest causes of acute kidney injury comprising 25 cases each (30%). The number of ATN is higher in this study than previous studies by Haas *et al* (2000) and López-Gómez *et al* (2008). This may be because of low threshold to perform kidney biopsy in suspected AKI in our setup. Many of these patients had septicemia. ATN constituted 23% of 184 cases and 50% of 40 cases of septic AKI studied by Langenberger *et al* (2008) and Leon *et al* (2006).

Among glomerular causes, crescentic glomerulonephritis was the most frequent cause of acute kidney injury with ANCA positivity in two patients. Immunofluorescence or electron microscopic examination could not be done which are the lacunae of this study.

One patient was post renal transplant and histopathology showed features of acute interstitial nephritis. According to Colvin (1996) the renal biopsy remains the most definitive and reliable diagnostic test for graft rejection, non-rejection injury and recurrent primary disease. Four patients had hemolytic uremic syndrome (HUS) in our study. Morel-Maroger *et al* (1979) in their study of 20 cases of HUS recommend a renal biopsy to be performed early, because the overall prognosis and the therapeutic attitude will entirely result from the renal biopsy findings.

Collapsing glomerulopathy and cast nephropathy due to myeloma represented one case each in this study. Collapsing glomerulopathy was seen in young HIV negative patient, which is a rare finding.

Acute cortical necrosis was seen in four patients in this study and three were young females in the post-partum period. This may be due to poor obstetrical services in the developing countries. (Bentata *et al*, 2012)

## CONCLUSION

The patient population in our study is not truly representative of the overall population who develop acute kidney injury because many patients with strong suspicion or evidence of ischemic or toxic ATN, obstructive nephropathy, acute pyelonephritis, and drug induced interstitial nephritis, do not undergo a renal biopsy and are treated on the basis of the clinical diagnosis. Yet, our study of 84 cases carried out in a tertiary healthcare center in North India proves that renal biopsy can be an adjuvant diagnostic modality in identifying the underlying renal lesions and aiding the diagnosis and treatment of acute kidney injury. On comparing clinical and biopsy diagnoses we found that a renal biopsy is needed for accurate diagnosis of the renal lesions present in a considerable number of AKI cases and in unearthing severe yet potentially treatable causes which would aid in provision of appropriate treatment to restore and preserve renal function and decrease the risk for dialysis dependence and death in patients with AKI. Immunofluorescence and electron microscopic examination could not be done which is the lacuna of this study.

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