# Significance of Histological variables in Acute Endocapillary Proliferative Glomerulonephritis in Adults

Authors
**P.C. Muraleedharan[1], N.K. Supriya[2], K P Aravindan[3], M. Sreelatha[4]**
Calicut University
Email: *drmuralipc@gmail.com*

**Abstract**

**Background-** *The prognosis of diffuse endocapillary proliferative glomerulonephritis of post infectious etiology in adults is variable with a significant proportion of patients having an adverse outcome. It would be useful if the disease outcome could be predicted by histological variables in the initial renal biopsy.*

**Objectives-** *a) To compare the clinical outcome of patients with infection related glomerulonephritis having different clinical and histological parameters at the time of initial renal biopsy.  b) To construct a scoring system capable of predicting cases with bad outcome.*

**Methods-** *Design: Retrospective cohort study done at Government Medical College Kozhikode from January 2004 to June 2008. The status of patients diagnosed to have diffuse endocapillary proliferative glomerulonephritis  in renal biopsy were collected by noting clinical symptoms, blood pressure, serum creatinine and urine routine findings. Statistical analysis were conducted using SPSS version 10.The patients were grouped into good and poor outcome groups based on clinical and laboratory findings at the end of a minimum period of six months follow up. Good outcome group had complete resolution or only minor urinary abnormalities and poor outcome group included patients who died due to disease or had either persistence of significant urinary abnormalities or a serum creatinine of 2 mg/dl or greater. Histopathological parameters were semi quantitatively graded and these along  with clinical parameters were compared between two groups.  The clinical and histological variables that were significantly different between the two outcome groups were used to construct a predictive scoring system.*

**Results-** *Of the 56 biopsies diagnosed as diffuse endocapillary proliferative glomerulonephritis there were 34 cases in which adequate follow up was available.  9 cases belonged to the poor outcome (26.5%) and rest  to the  good outcome group .The  variables that  differed significantly in the two groups  were S Creatinine (p=0.006), Crescents (p=0.002), Glomerular sclerosis (p=.001) and Interstitial fibrosis (p=0.0001)*

*Serum creatinine values and the grades of three histological parameters were added up for a predictive score.  Predictive scores ≥ 7 had a sensitivity of 0.89 and a specificity of 0.96 for predicting cases with adverse outcome.*

**Conclusions-** *Initial serum creatinine and selected graded histological parameters on renal biopsy done at the outset can predict eventual outcome of diffuse endocapillary proliferative glomerulonephritis with a high sensitivity and specificity*

## Introduction

Post infectious glomerulonephritis is a disease showing marked change in epidemiology, etiology and clinical presentation. Till three decades ago it was a disease of childhood. Its incidence has declined in children but is presently showing definite a rise among adults.[1,2] Alcoholism ,diabetes and immunosuppression have been detected as predisposing factors for the disease in adults. The most common etiology of post-infectious glomerulonephritis was group A β hemolytic streptococcus which is being replaced by staphylococci, gram negative bacilli and viruses.[3] In India diffuse proliferative glomerulonephritis comprises 8.1% of all biopsy proven kidney diseases and  a post infectious etiology represent 73% of acute glomerulo-nephritis in elderly.[4,5]

The mortality and long term complications of post infectious glomerulonephritis are more in adults compared to children. Approximately 95% of post infectious glomerulonephritis in children show full recovery of renal function within 3–4 weeks. Resolution of the clinical symptoms in children is also associated with reduction in the inflammatory changes at the tissue level. The proliferation and neutrophilic infiltration of glomeruli as well as the number of immune deposits decreases, both of which can be visualized by light and electron microscopy respectively.[1,2,5] In contrast to this, about 8–54% of adult  patients develop persistent renal function abnormalities and 4–33% progress to end stage renal disease .[6]

In the current study we have evaluated histologic parameters and semi quantitatively graded them for their capacity to predict the outcome of post infectious glomerulonephritis in adults. A scoring system for prognosticating the disease was also constructed.

## Objectives of the Study

- To evaluate the clinical outcome of adult patients diagnosed by renal biopsy as Diffuse Endocapillary Proliferative Glomerulonephritis in the Nephrology department of Calicut Medical College in a Five year period.
- To compare the clinical outcome of patients having different clinical and histological parameters at the time of initial renal biopsy.
- To construct a scoring system capable of predicting cases with bad outcome.

## Materials and Methods

It is a retrospective cohort study. 56 patients admitted to the Nephrology Department, Medical College, Calicut between January 2004 and June 2008 following an acute nephritic/ nephrotic episode and diagnosed to have diffuse endocapillary proliferative glomerulonephritis by renal biopsy were included in the study. All known primary causes other than post-infectious glomerulonephritis were excluded but co-existent diabetic nephropathy will not be exclusion.

## Initial Clinical evaluation

The medical records were reviewed and the relevant information at the time of the renal biopsy was recorded like age, sex, presence or absence of hypertension, 24 hour urine protein excretion, serum creatinine and urine microscopy .This was done to assess the disease outcome of the patients. Hypertension was defined as a blood pressure > 140/90 mm Hg or the use of antihypertensive agents.

## Histopathological examination

Histological grading was done by an observer (Principal investigator) blind to the clinical status of the patient.* Grading was performed  by assigning points (0 to 3) for a number of glomerular, interstitial, and vascular features in the renal biopsy and is described in Table 1

**Table.1** Histological grading of glomerular,tubulointerstitial & vascular parameters

| | | | |
|---|---|---|---|
| *Glomeruli* | | | |
| 1 | Cellularity | 100 - 150 cells | 1 |
| | | 151- 200 | 2 |
| | | >200 | 3 |
| 2 | Polymorphs in the tuft | 3 – 5 | 1 |
| | | 6 – 20 | 2 |
| | | >20 | 3 |
| 3 | Glomerular sclerosis | Absent | 0 |
| | | Less than 25% of glomeruli | 1 |
| | | 26 to 50% of glomeruli | 2 |
| | | >50% of glomeruli | 3 |
| 4 | Cellular crescents | Absent | 0 |
| | | Less than 25% of glomeruli | 1 |
| | | 26 to 50% of glomeruli | 2 |
| | | >50% of glomeruli | 3 |
| 5 | Tuft necrosis | Absent | 0 |
| | | Present in <25% | 1 |
| | | Present in 25-50% | 2 |
| | | Present in >50% | 3 |
| *Tubulointerstitial compartment* | | | |
| 1 | Interstitial fibrosis | Absent | 0 |
| | | Involving less than 25% of the biopsy area | 1 |
| | | Involving 26 to 50% of the biopsy area | 2 |
| | | Involving > 50% of the biopsy area | 3 |
| 2 | Interstitial inflammatory infiltrate | Absent | 0 |
| | | Involving less than 25% of the biopsy area | 1 |
| | | Involving 26 to 50% of the biopsy area | 2 |
| | | Involving > 50% of the biopsy area | 3 |
| 3 | Presence of RBC or proteinaceous casts | Absent | 0 |
| | | Isolated | 1 |
| | | Present in up to 10% of tubules | 2 |
| | | Present in > 10% of tubules | 3 |
| 4 | Interstitial edema (extent of tubular separation that was not the result of interstitial fibrosis) | Back-to-back tubules | 0 |
| | | Mild focal separation of tubules | 1 |
| | | Diffuse mild or focal moderate separation of tubules | 2 |
| | | TBM diffusely separated by the thickness of a tubular epithelial cell | 3 |
| 4 | Tubular dilation | Absent | 0 |
| | | Mild | 1 |
| | | Moderate (Associated with flattening of the tubular epithelium) | 2 |
| | | Severe (Tubular diameter exceeding that of glomeruli) | 3 |
| 5 | Tubular epithelial vacuolization | Absent | 0 |
| | | Mild and focal | 1 |
| | | Diffuse mild or focal moderate | 2 |
| | | Severe and diffuse | 3 |
| *Vessels* | | | |
| 1 | Reduction in vascular caliber because of sclerosis or hya!inization | Absent | 0 |
| | | Less than 25% of luminal diameter | 1 |
| | | 26 to 75% diameter | 2 |
| | | Greater than 75% | 3 |
| 2 | Intimal thickening (assessed by comparing thickness of intima relative to total medial thickness) | Normal | 0 |
| | | Intimal thickness < 25% medial thickness | 1 |
| | | Intimal thickness 25≤50% of medial thickness | 2 |
| | | Intimal thickness > 50% medial thickness | 3 |
| 3 | Medial hypertrophy (comparing thickness of the muscular wall relative to the vascular caliber) | Normal | 0 |
| | | Mild | 1 |
| | | Moderate | 2 |
| | | Severe | 3 |

*Scores for each individual component, composite scores were obtained for

**Glomerular compartment:** five component scores for a maximum score of 15.

**Interstitial compartment:** six components for a maximum of 18

**Vascular compartment:** three components for a maximum of 9

**Overall histopathologic score:** 14 components for a maximum score of 42

The patients were followed-up in the nephrology Out-Patient clinic. Freshly voided midstream urine sample and 4 ml of blood were collected. Urine protein estimation was done on a filtered sample by the heat and acetic acid test and graded from 0 to 4+.Urine microscopy was also done.

### Data analysis

For the analysis, patients were divided into two groups based on findings *after* a minimum of six months follow up:

*Good prognosis group*: Complete resolution or only minor urinary abnormalities.

*Poor prognosis group*: Death due to disease or persistence of significant urinary abnormalities (Heavy proteinuria ie. 3-4+ / red cells >30 hpf of centrifuged urine), serum creatinine of ≥2 mg/dl .
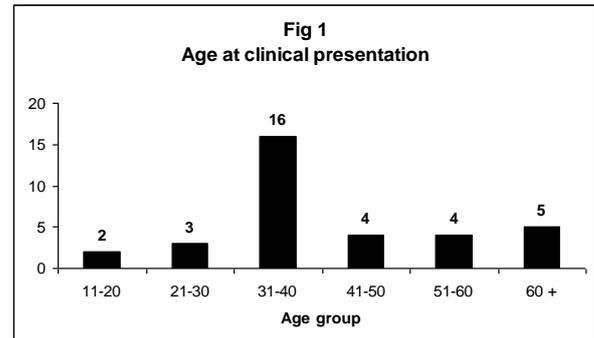
The groups were compared for clinical and histopathological variables.

The clinical and histological variables that were significantly different between the two outcome groups were added up to give a predictive score. The optimum cut-off value to predict the cases with adverse outcome was determined by ascertaining the best sensitivity, specificity and predictive values. Statistical findings were tabulated using Microsoft excel. Statistical analysis were conducted using SPSS version 10.(SPSS Inc,Chicago, USA).

### Results

**Patient data-** Of the 56 biopsies diagnosed as diffuse endocapillary glomerulonephritis there were 34 cases in which adequate follow up was available. The male female ratio was 1.1 and the mean age 42.6 years. The minimum follow-up period was 6 months.

9 cases (26.5%) belonged to the poor and 25 cases belonged to good prognosis group. There were 2 deaths due to disease among the 34 patients followed up (5.9%). Heavy proteinuria persisted in 2 patients and 5 patients (17.6%) had creatinine levels of ≥2 mg/dl.



**Fig 1
Age at clinical presentation**

The most common age of presentation was the fourth decade (Figure 1). The typical histopathological appearance of glomeruli is given in Figure 2. Haematuria and proteinuria were the most common presentation (Figure 3). There were no difference in the clinical features like age,evidence of hypertension ,proteinuria or haematuria between the good and poor prognostic group. But the poor prognostic group had a higher serum creatinine at presentation (Table-2).
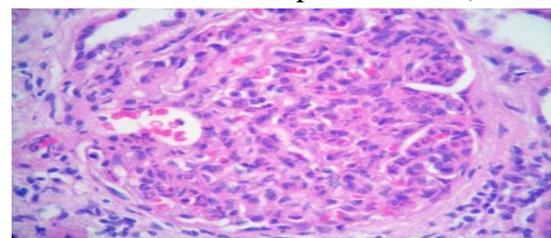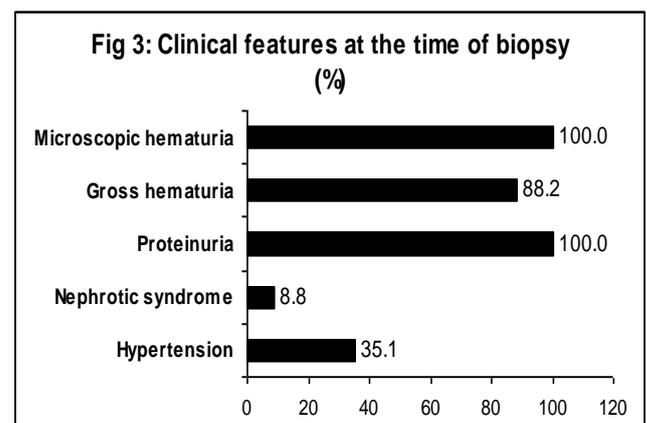


**Fig 2:** A hypercellular glomerulus with endocapillary proliferation H&E x 400



**Fig 3: Clinical features at the time of biopsy (%)**

| | |
|---|---|
| Microscopic hematuria | 100.0 |
| Gross hematuria | 88.2 |
| Proteinuria | 100.0 |
| Nephrotic syndrome | 8.8 |
| Hypertension | 35.1 |

Of the histopathological changes noted in the biopsy (Figure-2),the severity of inflammation in

the glomerular compartment asessed by mesangial cellularity , the neutrophil numbers or tuft necrosis and presence of interstitial inflammation did not have any significant correlation with outcome of the disease.But the presence of cellular crescents in the biopsy correlated significantly with the patient outcome. Glomerular sclerosis,tubular atrophy,interstitial fibrosis and vascular sclerosis where taken as the histopathological evidence of chronic kidney injury (Table 1&2). The various histological tubular and interstitial parameters are given in Figures 5 & 6.

**Table 2-** Risk estimates of clinical and histological predictors for poor outcome ($\chi^2$ test)

| Parameter | Odds Ratio | 95% CI | P |
|---|---|---|---|
| Age >40 years | 0.36 | 0.06 - 2.1 | 0.72 |
| Heavy proteinuria ($\geq$ 3+) | 3.6 | 0.71 – 17.7 | 0.11 |
| Heavy hematuria ($\geq$ 30 cells/hpf) | 0.75 | 0.14 – 4.0 | 0.73 |
| S Creatinine >3 mg/dl | 6.2 | 1.1 – 36.6 | 0.03 |
| Glomerular cellularity ($\geq$ grade 2) | 0.62 | 0.12 – 2.9 | 0.29 |
| Presence of Crescents | 14.4 | 1.2 – 168.5 | 0.01 |
| Glomerular sclerosis ($\geq$ grade 1) | Undefined | 5.1 - $\infty$ | <0.0005 |
| Interstitial fibrosis ($\geq$ grade 1) | 30.0 | 2.7 – 328.6 | 0.0005 |
| Interstitial inflammation ($\geq$ grade 2) | 3.0 | 0.6 – 14.9 | 0.17 |
| Vascular medial hypertrophy ($\geq$ grade 2) | 3.2 | 0.6 – 16.5 | 0.15 |

**Table 3** Relation of graded clinical and histological parameters to outcome (Simple linear regression)

| Parameter | Correlation coefficient | P |
|---|---|---|
| Age | 0.00 | 0.856 |
| Hypertension | 0.05 | 0.213 |
| Proteinuria | 0.02 | 0.431 |
| Hematuria | 0.03 | 0.377 |
| S Creatinine | 0.23 | 0.006 |
| Glomerular cellularity | 0.02 | 0.484 |
| Crescents | 0.25 | 0.002 |
| Glomerular sclerosis | 0.30 | 0.001 |
| Interstitial fibrosis | 0.38 | 0.0001 |
| Interstitial inflammation | 0.05 | 0.224 |
| Vascular medial hypertrophy | 0.00 | 0.900 |



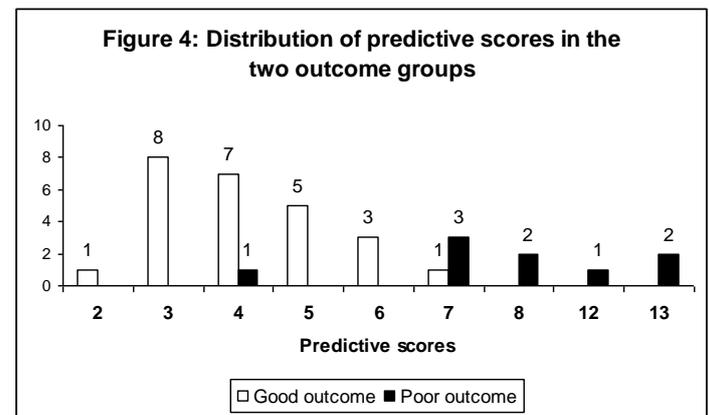**Figure 4: Distribution of predictive scores in the two outcome groups**

**Table 4** Diagnostic efficacy parameters for prediction of poor prognosis with different cut off predictive scores

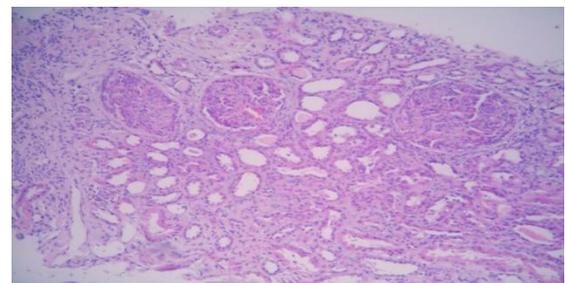| Parameter | Cut-off | | | |
|---|---|---|---|---|
| | $\geq 5$ | $\geq 6$ | $\geq 7$ | $\geq 8$ |
| Sensitivity | 0.89 | 0.89 | 0.89 | 0.56 |
| Specificity | 0.68 | 0.84 | 0.96 | 1.00 |
| Positive Predictive Value | 0.50 | 0.67 | 0.89 | 1.00 |
| Negative Predictive Value | 0.94 | 0.95 | 0.96 | 0.86 |



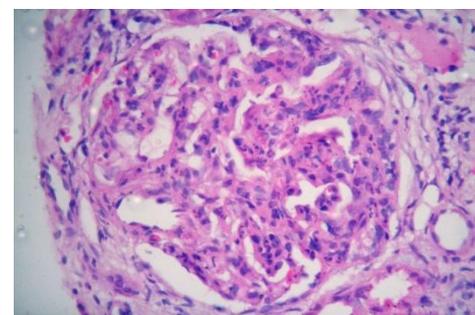**Figure-5** Grade 2 interstitial fibrosis H&E x 100



**Figure-6** Thin cellular crescent seen on the right side of the tuft. H&E x 400

### Discussion

Majority of both adults and children have a good prognosis and show complete recovery.[6,7] Around 26.4% of patients had a poor outcome in our study .This may be due to a short term follow up of six

months.[7] Most of the previous studies have shown that the renal dysfunction takes a longer time to revert back to normal in adults as compared to children.[8,9]

Age and initial heavy proteinuria or even nephrotic syndrome did not have any bearing on ultimate prognosis. On the other hand none with an initial creatinine less than 2.5 mg /dl had an adverse outcome. According to Vogl et al, cases with an initial nephrotic syndrome had a significantly poorer long-term prognosis,but the initial elevation of serum creatinine concentration did not influence the long-term prognosis.[11]Other studies have also shown that the long term prognosis of acute nephritis in adults show a significant correlation with age and proteinuria.[3]

Most cases of acute nephritis in adults unlike children tend to be biopsied in order to rule out the secondary causes of diffuse proliferative glomerulonephritis. Semi quantitative grading of various changes in renal biopsies have been in use in conditions like SLE & Ig A nephropathy for patient prognostication and treatment. In this study, we have tried to predict those cases of post infectious glomerulonephritis with adverse outcome by using a grading system combining the clinical and histological parameters which differed significantly between the groups with good and poor outcomes.

The histological variables that were found to significantly differ in the good and poor outcome groups were the presence of crescents, degree of glomerular sclerosis and interstitial fibrosis.[12] The last two are quite logical since glomerular sclerosis and interstitial fibrosis are irreversible changes. However these changes are not common in a pure diffuse endocapillary glomerulone-phritis. More than 25% glomerular sclerosis or interstitial fibrosis were seen in only five cases each in our material. Age and pre-existing tubulointerstitial disease are possible causes for these changes in the kidney which may be subsequently affected by infectious glomeulonephritis.

Crescents have been found to positively correlate with adverse outcome in other studies as well.[3,9,10] Crescentic glomerulonephritis can have a post-infectious etiology. However, such cases have not been included in our study.

The degree of glomerular tuft hypercellularity, the amount of neutrophil infiltration of glomeruli, glomerular necrosis, adhesions and glomerular capillary thromboses have all been attributed to worse outcome in different studies. [13] None of these were found to be significant in our study.

The severity of interstitial inflammation in renal biopsies of patients with diffuse proliferative glomerulonephritis were associated with poor outcome.[13] The Odds Ratio for worse outcome with increase in interstitial inflammatory infiltrate was 3.0 in our study. But this was not statistically significant (p=0.17), probably because of small number of cases.

Vascular changes such as arteriolar sclerosis and arterial sclerosis have also been suggested to be a harbinger of poor prognosis in some studies. These too have not been found to be significant in our series.

Our cases are defined by histology ie. diffuse endocapillary proliferation. It is presumed that these cases are post-infectious. The infectious etiology has not been proved. But we have excluded other causes like IgA nephropathy and systemic lupus erythematosis by appropriate tests. It is still possible that cases due to some other non infectious cause have been included. However, these are likely to be very rare and not likely to affect the overall results.

We could obtain follow-up data in only about 60% of our patients. This could be serious flaw in studies that tried to determine the absolute prognosis and the proportion of patients eventually dying or developing renal failure. Indeed, the studies such as those of Baldwin et al[14] and Lewy et al[15] have been criticized on this account.[16] The problem is that the patients who have not been contacted are the ones more likely to have died. But this would not be as

problematical in studies such as ours which only aim at relative prognosis by group comparisons.

The novelty of the current study is in the formulation of a predictive scoring system incorporating selected clinical and histological parameters for prognosticating the outcome of diffuse endocapillary glomerulonephritis in adults. The system has a sensitivity of 0.89 and specificity of 0.96.

Ideally, the good prognosis group should comprise patients who have complete clinical, biochemical and pathological recovery as indicated by normal urine. But the minimum follow-up in our series is only six months. It is well known that minor urinary abnormalities can persist for longer periods in patients with post-infectious glomerulonephritis who have eventual complete recovery. So we have included those cases with only minor urinary abnormalities also in the good outcome group. Even though recent studies have shown that alcoholism, comorbidities like diabetes, tubulointerstitial diseases are associated with poor prognosis, these have not been examined in our patients.

## Conclusion

Of the 34 cases of diffuse endocapillary proliferative glomerulonephritis in which adequate follow up was available, the clinical and histopathological variables that were found to significantly differ in the good and poor outcome groups were only the serum creatinine levels at presentation , presence of cellular crescents ,glomerular sclerosis and interstitial fibrosis.

Initial serum creatinine and graded significant histopathological parameters specified above can predict eventual outcome of diffuse endocapillary proliferative glomerulonephritis with high sensitivity and specificity. The importance of knowing such poor prognostic markers in the basic light microscopic examination of kidney itself can help in  picking up patients who are at risk of progressing to a long term renal dysfunction and keeping them on close follow up.

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