# A 5-year retrospective study to determine the spectrum of crescentic glomerulonephritis in three tertiary hospitals in Gauteng Province, South Africa

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**Background.** Rapidly progressive glomerulonephritis is a clinical syndrome that results in rapid decline in kidney function over a period of weeks to months. Its histological hallmark is extensive crescent formation.
**Objective.** To determine the causes of crescentic glomerulonephritis (CGN) in the South African (SA) setting.
**Methods.** The number of kidney biopsies performed at three tertiary hospitals during the 5-year study period was determined. Demographic data and serological test results were recorded. The underlying disease process of each of the CGN cases was defined under the three immunopathological categories: anti-glomerular basement membrane disease; immune complex-mediated; and pauci-immune vasculitis.
**Results.** There were a total of 980 native kidney biopsies performed at the three tertiary hospitals, namely, Chris Hani Baragwanath Academic Hospital, Charlotte Maxeke Johannesburg Academic Hospital and Helen Joseph Hospital, in Gauteng Province, SA, between 1 January 2015 and 31 December 2019. There were 43 crescentic glomerulonephritidies (4.4%). The patients' ages ranged from 19 to 65 years, and 30 patients were female. The study comprised a majority of black patients (83.7%). Most CGN cases (39/43; 90.7%) were immune complex-mediated, and the remainder were anti-neutrophil cytoplasmic antibody mediated. The underlying cause of the 39 immune complex-mediated crescentic glomerulonephritides was lupus nephritis in 32 (82%) cases, post-infectious glomerulonephritis (PIGN) in 2 (5.1%), IgA nephropathy in 1 (2.6%) and 4 (10.2%) with an undetermined underlying cause.
**Conclusions.** This study revealed the predominant cause of CGN to be lupus nephritis in 82.1% of patients, followed by PIGN in 5.1%. The prevalence of CGN was 4.4%. This study emphasises the variation in aetiologies of CGN in sub-Saharan Africa.

**Keywords:** crescentic glomerulonephritis

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Rapidly progressive glomerulonephritis (RPGN) is a rare clinical syndrome that was first described in 1942 by Ellis.[1] It is caused by glomerulonephritis that results in rapid decline in kidney function over a period of weeks to months.[2] The clinical presentation is of nephritic syndrome with an active urinary sediment comprising haematuria, varying degrees of proteinuria, and inflammatory and other red cell casts.[3] Kidney function is usually deranged at time of presentation, and its severity varies in relation to the underlying cause.[1] Its histological hallmark is extensive crescent formation, and the term crescentic glomerulonephritis (CGN) refers to the histological manifestation of the clinical syndrome of RPGN (Fig. 1).

A crescent is a marker of severe glomerular injury. A crescent comprises at least two layers of inflammatory cells, including lymphocytes, neutrophils and macrophages, which is termed a cellular crescent. The crescent evolves during the process of scarring and becomes a mixture of inflammatory cells and collagen, which is referred to as a fibro-cellular crescent. As the crescent scars further, it is comprised of collagen, and is termed a fibrous crescent.[4] For the purposes of this study, CGN is defined by the presence of ≥50% crescents on light microscopy in a histologically adequate kidney biopsy. An adequate kidney biopsy sample is one that comprises the presence of 8 - 10 glomeruli on light microscopy.[5] It is a heterogeneous disease with various aetiologies leading to glomerular injury.[1]

The aetiology is divided into three broad categories based on the underlying immunopathological mechanism of glomerular injury, which is the categorisation used in this study:[1,6]

- Type I: anti-glomerular basement membrane (GBM) disease. It is characterised by the presence of anti-GBM antibodies directed against the non-collagenous domain of alpha 3 chain of type IV collagen. Anti-GBM disease constitutes 10 - 15% of RPGN cases.[6,7]
- Type II: immune complex-mediated RPGN (ICGN), such as lupus nephritis (LN), post-infectious glomerulonephritis (PIGN) and IgA nephropathy (IgAN), which account for 25 - 30% of the aetiology of CGN.[6,7]
- Type III: anti-neutrophil cytoplasmic antibody (ANCA)-associated (AAV) or pauci-immune vasculitis. This results in a necrotising glomerulonephritis, and is characterised by negative immunofluorescence. Myeloperoxidase (MPO) and proteinase 3 (PR3) are the most targeted antigens.[6,7]

In a meta-analysis of the epidemiology of various glomerulonephritidies in Africa, CGN comprised 2.0% of cases. The authors, however, noted that the meta-analysis might be inaccurate owing to poor categorisation. There was also no further elaboration on the underlying aetiology of the CGN.[8] Aetiologies vary according to age and race. ANCA-mediated CGN is cited as the most common cause of CGN, with a prevalence of 65 - 70%. Most such patients are aged >60 years, and white.[1,9] The estimated incidence of pauci-immune glomerulonephritis in the USA is 3.1 cases per million every year. Most of these patients are white, male and >65 years old. Most are ANCA positive. There is a higher incidence among white patients, with 1 - 2 cases per 100 000.[10]

In a large study from South India that looked at 8 645 biopsies, the most common mechanism of CGN was type II. In the type II category, the most common cause was LN (45%) followed by PIGN (24%) and IgAN (23%).[1] This was also shown in a large review from China, where LN made up 34% of cases of CGN, followed by IgAN, which made up 17%.[12]

A study conducted in then Natal Province of South Africa (SA) from 1981 to 1987 showed a prevalence of CGN of 2.7%. Black patients comprised 22.2% of the cases, and the main cause of CGN was PIGN at 29%.[13]

Recent studies of the characteristics of CGN in adults in SA have been sparse, although there is a recent retrospective study from paediatric nephrology at Chris Hani Baragwanath Academic Hospital, Johannesburg.[14] A study from Senegal found CGN in 5.3% of kidney biopsies conducted over 5 years. The aetiologies were mainly LN, in 32.5% of cases, followed by ANCA-related vasculitis (AAV) in 27.5% of cases, and infectious causes in 17.5% of cases.[2] This differs starkly from aetiologies of CGN in Western countries where the most common cause is AAV.[1]

It is anticipated that CGN may have other predominating causes in Africa, and it is essential to provide further data to contextualise this potentially devastating syndrome in the African setting.

## Methods

This was a retrospective observational study. The number of renal biopsies performed at three tertiary hospitals (Chris Hani Baragwanath Academic Hospital, Charlotte Maxeke Johannesburg Academic Hospital and Helen Joseph Hospital) between 1 January 2015 and 31 December 2019 was determined.

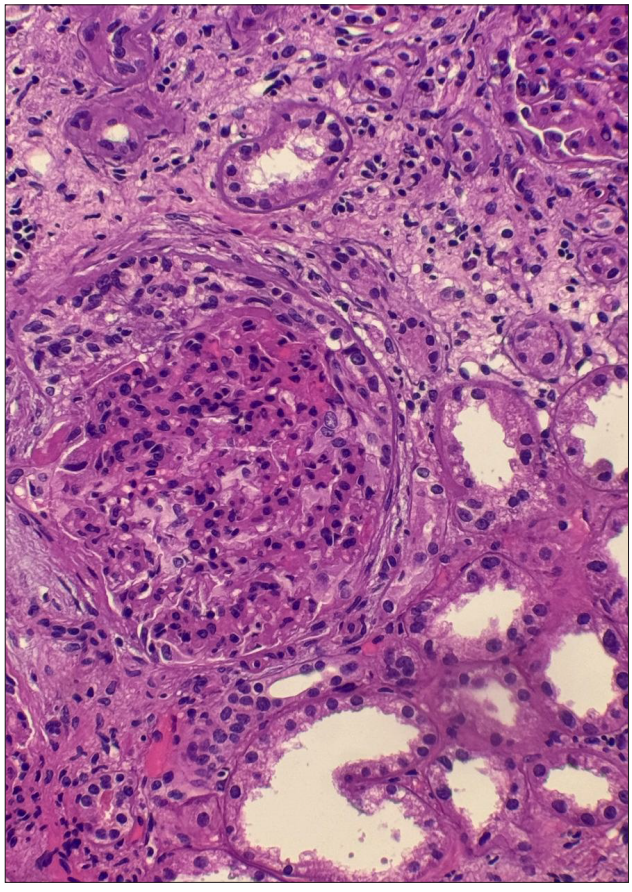

*Fig. 1. Cellular crescent on periodic acid-Schiff stain.*

All data were captured anonymously. Only patients >18 years old were included in the study. Cases were assigned numbers once the demographic information was captured, and the data were only accessible to the author.

Biopsies with ≥50% crescents on light microscopy were labelled CGN, and biopsies with <50% crescents from the total number of glomeruli on light microscopy were excluded from the study. The demographic data on age, gender and race were collected.

The serological test results of antinuclear antibody (ANA), perinuclear-ANCA (pANCA), cytoplasmic-ANCA (c-ANCA), anti-streptolysin O titre (ASOT), anti-GBM antibody, complement 3 and 4 levels (C3 and C4), HIV status with CD4 count and viral load, degree of proteinuria and haematuria, where available, were recorded.

The underlying cause of each of the CGN cases was recorded.

The data were expressed as *p*-values, mean and 95% confidence intervals (CIs). $P<0.05$ was regarded as statistically significant. Standard deviations (SDs) and interquartile ranges (IQRs) were used for continuous variables.

Ethical approval was granted by the University of the Witwatersrand Human Research Ethics Committee (Medical) (ref. no. M200450), and permission for data collection was obtained from the National Health Laboratory Services (NHLS).

## Results

There were a total of 1 513 biopsies performed at the three tertiary hospitals between 1 January 2015 and 31 December 2019. Of these, 133 biopsies were deemed suboptimal by the reporting pathologist for any meaningful diagnosis. The types of biopsies and the number of CGN cases are shown in Fig. 2.

There were 43 crescentic glomerulonephritidies (4.4%). The mean (SD) number of glomeruli from the 43 biopsies with CGN was 19.1 (9.94). There were two biopsies with <8 glomeruli on light microscopy. These biopsies had 6 and 7 glomeruli, respectively. The biopsy with 6 glomeruli showed cellular crescents in all 6 (100%), and the biopsy with 7 glomeruli showed cellular crescents in 5/7 (71.4%). Because of the significant number of crescents in these two biopsies, they were labelled CGN, despite a smaller number of glomeruli than needed to meet the definition of an adequate sample as defined by Najafian *et al*.[5]

The mean (SD) patient age was 30.7 (10.46) years. There were 13 male and 30 female patients. The patients comprised 36 black, 3 Indian, 3 white and 1 mixed-race patient (Table 1). Most (90.7%) cases were immune complex-mediated, and the remainder were ANCA mediated.

The underlying cause of the 39 immune complex-mediated crescentic glomerulonephritides was LN in 32 (82.1%) cases, PIGN in 2 (5.1%), IgAN in 1 (2.6%), and 4 (10.2%) with an undetermined underlying cause (Fig. 3).

The demographic data in relation to each cause of CGN are documented in Table 1.

The two cases of PIGN were secondary to post-streptococcal glomerulonephritis. One patient had an ASOT titre of 832 IU/mL and an antiDNase B titre of 918 IU/mL, and the other had an ASOT titre of 835 IU/mL.

Among the 4 cases of AAV, the serum antigen was myeloperoxidase (MPO) in 3 patients and proteinase 3 (PR3) in one.

Twenty-six patients presented with nephrotic range proteinuria (≥3 g). Data were missing for three patients.

Four patients were HIV positive, three had viral loads that were lower than detectable (<20 copies/mL) and one had a viral load of 200 073 copies/mL. The underlying aetiologies in these patients were LN in two patients, and one each of PIGN and ANCA-mediated GN. HIV status was missing for four patients.

## Discussion

RPGN is a rare kidney syndrome characterised by rapid decline in kidney function occurring over a period of weeks to months.[1,2] It is a heterogeneous clinical syndrome with various underlying aetiologies.[1]

In Okpechi *et al*.'s[8] meta-analysis, the prevalence of CGN was 2%. Our study showed more than double the prevalence, similar to the Senegalese study mentioned above.[2] This is likely a more accurate range, as there were shortcomings in the accuracy of the data in the Okpechi *et al*.[8] meta-analysis.

As expected from our clinical experience, the predominant aetiology was type II, which is immune complex-mediated, with the diagnosis being LN in most cases. This was also shown in the large meta-analysis by Okpechi *et al*.,[8] which showed LN to be the most prevalent cause of CGN, and the mean age at time of biopsy among adults <40 years. LN is predominant in black African females of childbearing age; therefore, these findings are in keeping with the demographic context.

The ages of the patients with ANCA-mediated GN were also lower than found in Western studies. This is in keeping with a large study looking at the clinical characteristics of African Americans with AAV, which found the age of diagnosis to be lower in the African American group compared with white patients.[15] African Americans were found to be MPO ANCA positive significantly more often than white patients.[15] This was also the finding in the present study, where three out of the four patients with AAV were MPO ANCA positive. Although the numbers are small in this study, it displays a similar trend to findings of larger studies.

The underlying causes of CGN in HIV-positive patients appear heterogeneous in this study. Large series have attributed up to 20% of kidney injury to immune complex-mediated glomerulonephritis in HIV-positive patients. This is confirmed by the recent pathological classification of HIV-related kidney diseases in the category of immune complex-mediated disease in HIV patients.[16] This category reasserts the findings of Nochy *et al*.'s[17] 1993 article, and emphasises the autoimmune work-up necessary in HIV-positive patients presenting with kidney dysfunction.[17]

The findings of this study and the Senegalese study[2] are starkly different from those of the Natal study from the 1980s[13] in terms of the underlying aetiology. The findings from that study lay bare the disparities in healthcare caused by the apartheid regime of the time. Black patients comprised the minority, and this was likely due to poor access to healthcare for black people at the time.

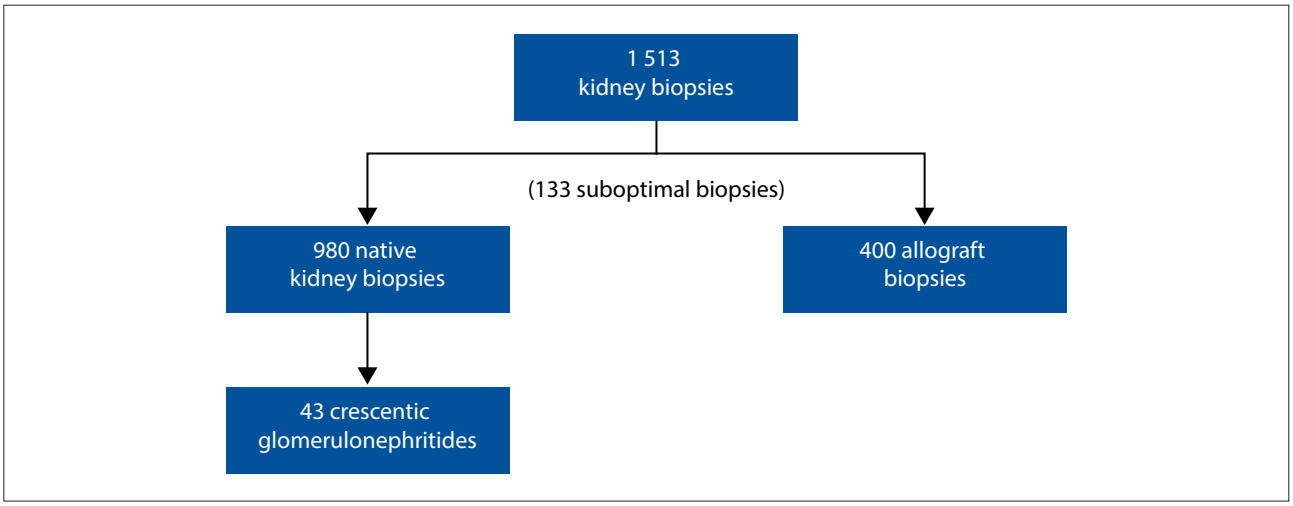


*Fig. 2. Number of biopsies included.*

**Table 1. Demographic data according to CGN aetiologies**

| | Cause of CGN, % | | | | |
|---|---|---|---|---|---|
| **Characteristic** | **LN** | **PIGN** | **ANCA vasculitis** | **IgAN** | **Undetermined** |
| Gender | | | | | |
| Male | 18.7 | 2.3 | 6.9 | 2.3 | 4.7 |
| Female | 81.3 | 2.3 | 2.3 | 0 | 4.7 |
| Race | | | | | |
| Black | 60.5 | 6.9 | 6.9 | 2.3 | 9.3 |
| White | 4.7 | 0 | 2.3 | 0 | 0 |
| Indian | 6.9 | 0 | 0 | 0 | 0 |
| Mixed | 2.3 | 0 | 0 | 0 | 0 |
| Age group, years | | | | | |
| 19 - 29 | 46.5 | 0 | 2.3 | 2.3 | 4.7 |
| 30 - 39 | 13.9 | 4.7 | 2.3 | 0 | 4.7 |
| 40 - 49 | 11.6 | 0 | 0 | 0 | 0 |
| 50 - 59 | 2.3 | 0 | 2.3 | 0 | 0 |
| ≥60 | 0 | 0 | 2.3 | 0 | 0 |

CGN = crescent glomerulonephritis; LN = lupus nephritis; PIGN = post-infectious glomerulonephritis; ANCA = anti-neutrophil cytoplasmic antibody; IgAN = IgA nephropathy.

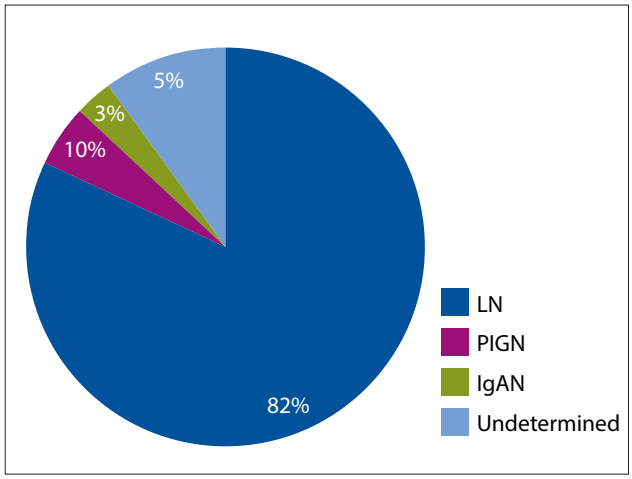


*Fig. 3. Immune complex-mediated glomerulonephritis. (LN = lupus nephritis; PIGN = post-infectious glomerulonephritis; IgAN = IgA nephropathy.)*

It is also interesting that PIGN was the most common cause of CGN in the Natal study. This is likely a result of limited access to antibiotics.

Recent studies confirm what we see every day in clinical practice in Africa, where most patients that present as RPGN are young black females with LN.

The Senegalese study was a retrospective study conducted over 5 years. The researchers found a prevalence of CGN of 5.3%. There was a predominance of female patients, and the mean age was 34 years.[2] The majority of the cases were immune mediated, with LN constituting the largest proportion of cases. This was followed by AAV and PIGN.[2]

The Senagalese study is similar to ours, which showed a similar prevalence of crescentic GN at 4.4%. The majority of the patients were female, with a mean age of 31 years. Our study also showed the same major immune-mediated underlying mechanism of injury, specifically in terms of LN being the leading diagnosis.

This prevalence (in the Senegalese and the present study) is more than double the prevalence figures from South Asia and China. The study from South Asia reviewed 8 645 kidney biopsies, and of these 200 (2.3%) showed CGN.[11] The Chinese study included 33 747 patients, of whom 528 (1.6%) showed CGN.[12] The most common mechanism of CGN in these studies was also type II, with LN the leading cause in both.

The incidence and prevalence of systemic lupus erythematosus are highest among young women and among black, Hispanic and Asian populations worldwide.[18] In a review by Barber *et al.*,[18] it was found that LN comprised up to 29% of all kidney biopsies performed in Africa. LN also tends to have a more aggressive histological picture and a poorer outcome in black than in white patients.[19] This is in keeping with the results of our study, where the majority of CGN was secondary to LN and more prevalent in black female patients.

These findings contrast with findings from Western data, where the predominant cause of CGN is type III pauci-immune vasculitis.[1,10]

### Study limitations

CGN is a rare condition, and therefore although this study looked at 980 native kidney biopsies, the prevalence remained small with a total of 43 cases, which was a limiting factor of the study.

Owing to the study's retrospective nature, not all results were available for every patient.

This study focused on histopathological and biochemical data from the NHLS database. Future studies incorporating this information with clinical data from the individual hospitals would add to the clinical context of the study.

## Conclusion

This study provides additional data on the features of CGN in the African setting. It aims to build on the sparse research currently available on this topic, and to emphasise the importance of recognising the clinical syndrome of RPGN.

**Data availability.** The data used for this study are available from the author on request.

**Declaration.** None.

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**Author contributions.** Sole author.

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**Conflicts of interest.** None.

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