Frontiers in Health Informatics
ISSN-Online: 2676-7104
www.healthinformaticsjournal.com
2024; Vol 13: Issue 8
Open Access

Infection-Related Glomerulonephritis: Clinicopathological Profile And Outcomes From A Tertiary Care Centre In South India

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Cite this paper as: Dr. Permi Vamshi Dharan,Dr. Raghukanth Reddy ,Dr. Manjunath S Shetty,Dr. Kiran K.K,Dr. Manoj C ,Dr. Sourabha R (2024). Infection-Related Glomerulonephritis: Clinicopathological Profile And Outcomes From A Tertiary Care Centre In South India. *Frontiers in Health Informatics*, *13 (8) 3745-3758*

ABSTRACT

Introduction

Infection-related glomerulonephritis (IRGN) is an immunological renal damage resulting from current or recent infections. As the landscape of IRGN has evolved, renal biopsy has become crucial for diagnosing and distinguishing this condition from others, as well as for predicting long-term consequences. The aim of present study is to assess the clinicopathological profile and outcomes of infection related glomerulonephritis in South India from a tertiary care center.

Material and methods

This retrospective study collected data of 73 patients diagnosed with IGRN with mean follow-up of 1 year. Demographic, clinical, laboratory, histological parameters and outcomes observed were assessed.

Results

The mean age of patients was 44.1±17.6 years. Number of female patients were 30.1% and male patients were 69.9%. 78.1% had low complement level C3. 56.20% had acute GN while 17.8% had RPGN presentation. The most common site of infection was skin and soft tissue (32.90%). The most common organism found in the culture was klebsiella

pneumonia (4.1%). The mean creatinine at presentation was 3.10 ± 2.5 mg/dl, with an estimated glomerular filtration rate (eGFR) of 47.26 ± 39.82 ml/min/1.73 m² and an average proteinuria of 3.14 ± 1.4 gm/24h. 100% of the samples showed an endocapillary proliferative pattern, 97.9% showed a mesangial proliferative pattern, and 6.1% showed MPGN pattern. 80.8% had an exudative neutrophilic infiltration. C3 was the universal immunological reactant with IgG being the most common immunoglobulin (69.4%) and IgM being the least common (4.1%), 10% of biopsies had IgA codominant pattern and in 4% biopsies full house pattern was seen. 75.3% recovered completely, in 54.8% hypertension persisted for more than 6 months and persistent proteinuria was seen in 27.4 % patients. 27.3% progressed to CKD while 10.9% remained dialysis dependent at the end of 1 year. Age >40 years (p=0.001), alcohol intake (p=0.001), peak creatinine >1.5 mg/dl (p=0.001) and RRT required (p-0.001) were associated with failure to attain complete recovery and were identified as independent risk factors in our study.

Conclusion
IRGN is a common clinical entity in adults with the potential for adverse renal and survival outcomes.

Keywords
Biopsy, Clinical Profile, Immunoglobulin, Infection-Related Glomerulonephritis, Outcomes

INTRODUCTION

Infection-related glomerulonephritis (IRGN) illustrates immunological renal injury caused by non-renal infections. This disease has evolved over the years with regard to its epidemiology, clinical presentation, etiological agents, histological attributes, immunofluorescence profile, and final outcome.[1] Adult IRGN is associated with a wider array of non-streptococcal infections, especially staphylococci and Gram-negative bacteria.[2-4] It may be associated with a wider variety of infected areas (beyond the skin and upper respiratory tract), with certain patients displaying infection at multiple locations.[5] IRGN without an identifiable infectious cause may be associated with undetected visceral or deep-seated abscesses,[6-9] requiring a comprehensive examination for any concealed primary infection source.

Adult IRGN, especially in the elderly, correlates with an increased prevalence of underlying comorbidities such as diabetes mellitus, liver disease, cancer, and other immunocompromised conditions. The presence of these factors has been shown to result in adverse renal outcomes.[10] They are at a heightened risk of encountering severe consequences, such as nephrotic range proteinuria, dialysis-dependent renal failure, congestive heart failure and mortality.[11] One variant of this illness, known as immunoglobulin A (IgA)-dominant immune complex-mediated renal glomerular nephritis (IRGN), is more commonly seen in older adults. In IgA-dominant IRGN, IgA is the only or predominate immunoglobulin, as opposed to traditional IRGN, which is marked by glomerular deposition of IgG and C3 or specifically C3. [12]

Furthermore, as the landscape of IRGN has progressed over the years, renal biopsy is essential for differentiating this condition from other mimickers and assists in prognostication and outlining long-term outcomes.[13] The purpose of the current study is to evaluate the clinicopathological characteristics and outcomes of infection-related glomerulonephritis in South India from a tertiary care center.

MATERIAL AND METHODS

This retrospective observational study was carried out in the nephrology department of a tertiary care private medical

college from January 2020 to August 2023. Through simple random sampling patients diagnosed with IGRN were selected on the basis of inclusion and exclusion criteria.

Inclusion criteria:

- Patients fulfilling at least two out of each of the following three criteria:
  - Clinical or laboratory documentation of preceding or ongoing infection.
  - Low levels of complement C3 and C4 at the time of presentation
  - Active urinary sediments (red blood cells [RBCs], RBC casts, and white blood cell casts) present with or without renal impairment

Exclusion criteria:

- Patients displaying clinical or biochemical signs of secondary glomerulonephritis.

Data on clinical symptoms and examination findings were obtained from patient case records. Laboratory measures such as urinalysis, complete hemogram, renal function test, liver function test, complement levels, Anti Streptolysin O (ASO) titer, blood cultures, and urine cultures, as well as tissue, pus, and throat swab cultures, were obtained in relevant instances. Data on the indications for renal biopsy, as well as biopsy findings, were obtained from patient's case records. Follow-up data comprise both clinical examination and laboratory parameters that were acquired from patient outpatient/inpatient records at 1 month, 3 months, 6 months, and one year after discharge.

Statistical analysis- All continuous variables were expressed as mean with standard deviation or median, where applicable. The Student's t-test was employed to compare means. Fischer's test and Chi-square analysis were employed for univariate analysis, when applicable. Binomial logistic regression was utilized for multivariate analysis. A two-tailed P value below 0.05 was deemed significant. The analysis was conducted using Microsoft Excel and IBM-SPSS software.

RESULTS

A total of 106 patients were screened, of which 73 were confirmed to have IRGN and had a minimum follow-up of one year. Of the 73 patients, 49 were biopsy proven and rest 24 were diagnosed by clinical profile and serology.

Patient demographics and clinical characteristics:

The mean age of the patients was 44.1±17.6 years. Female patients accounted for 30.1% of the total, while male patients made up 69.9%. The percentage of adults above the age of 18 was 86.3%. The proportion of people living in rural areas was 72.6%. 38.4% of patients smoked, while 34.3 % consumed alcohol. The highest number of patients were reported in July (21.9 %). 60.3% had a documented prior infection. The average time interval between the prior infection and GN was 14.8 days. Trends of patients with IRGN with respect to age and month of presentation is shown in figure 1 and 2
Patients were categorised into one of four presentations: acute glomerulonephritis, nephrotic syndrome, rapidly progressive glomerulonephritis (RPGN), or acute on chronic kidney disease (CKD). Majority of patients had acute glomerulonephritis(56.20%), while RPGN was seen in 17.8%, 16.4% had acute on CKD presentation while 9.60% presented with nephrotic syndrome as shown in Figure 3. Almost 97.3% had oedema at presentation, 72.6% had AKI, only 11% had macroscopic hematuria, while 68.5% had microscopic hematuria, 41.1% had fever, 67.1% had dyspnea, 26% required RRT, 93.15% had hypertension at presentation, 31.5% had diabetes, 4.1% had IHD, 12.3% had CKD,

21.9% were taking NSAID as shown in Table 1.

In patients with documented infection prior to renal failure, the predominant site of infection was skin and soft tissue, followed by sore throat; in 38.4% of cases, no identifiable source of infection was found, as illustrated in Table 2. Microbiological confirmation was possible in only 9 cases (12.30%), whilst no organism could be isolated in 87.30% of patients, as illustrated in Table 3.

Laboratory parameters:

The mean creatinine at presentation was 3.10 ± 2.5 mg/dl, with an estimated glomerular filtration rate (eGFR) of 47.26 ± 39.82 ml/min/1.73 m² and an average proteinuria of 3.14 ± 1.4 gm/24 h. At presentation, 78.1% of cases exhibited a diminished complement level (C3), whilst 35.6% exhibited concomitant low levels of both C3 and C4, as illustrated in Table 4.

Table 1: Demographic data and clinical presentation of patients

Variable		Values
Mean age (years)		44.1 ±17.6
Gender	Male	51 (69.9)
	Female	22 (30.1)
Number of adults >18 years of age		63 (86.3)
Locality	Urban	20 (27.4)
	Rural	53 (72.6)
Documented preceding infection		44 (60.3)
Average time interval between preceding infection and GN (days)		14.8±7.1
Smoking		28 (38.4)
Alcohol		25 (34.3)
Oedema		71 (97.3)
AKI		53 (72.6)
Macroscopic hematuria		8 (11)
Microscopic hematuria		50 (68.5)
Fever		30 (41.1)
Dyspnea		49 (67.1)
Requiring RRT		19 (26)
Hypertension		68 (93.15)
SBP>160		16 (21.9)
SBP>200		7 (9.6)
Diabetes		23 (31.5)
Ischemic heart disease		3 (4.1)
CKD		9 (12.3)
CVA		0
NSAID intake		16 (21.9)

Figure 1: distribution of cases with repect to age

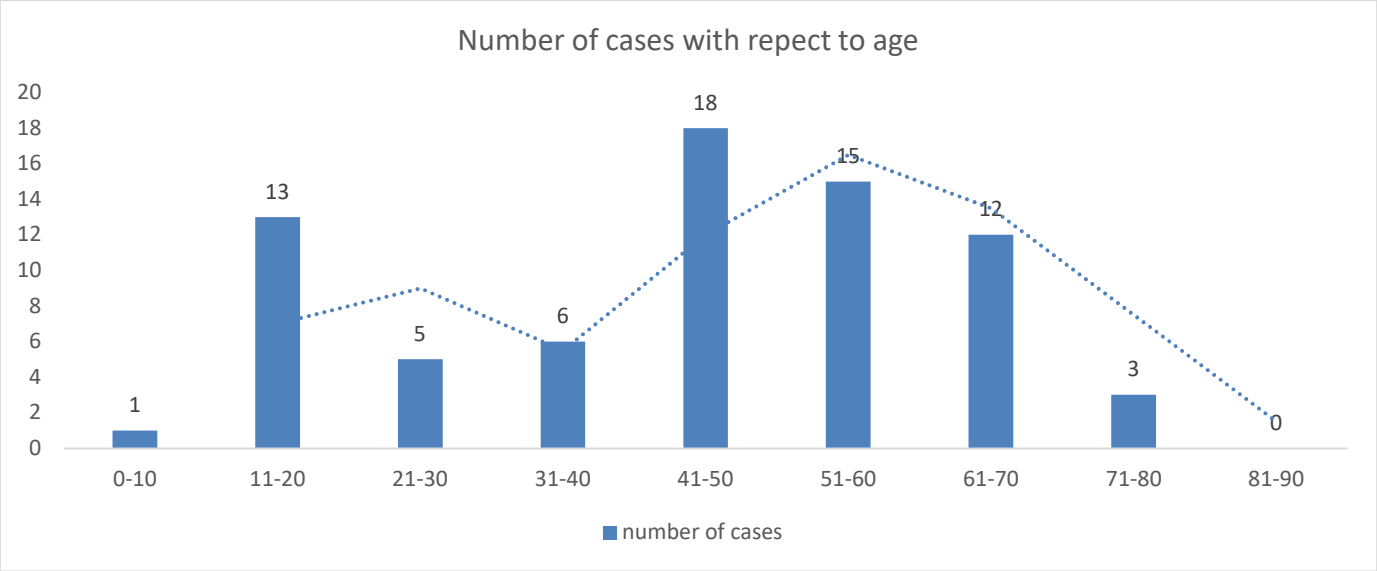

Figure 2: distribution of cases with respect to time period

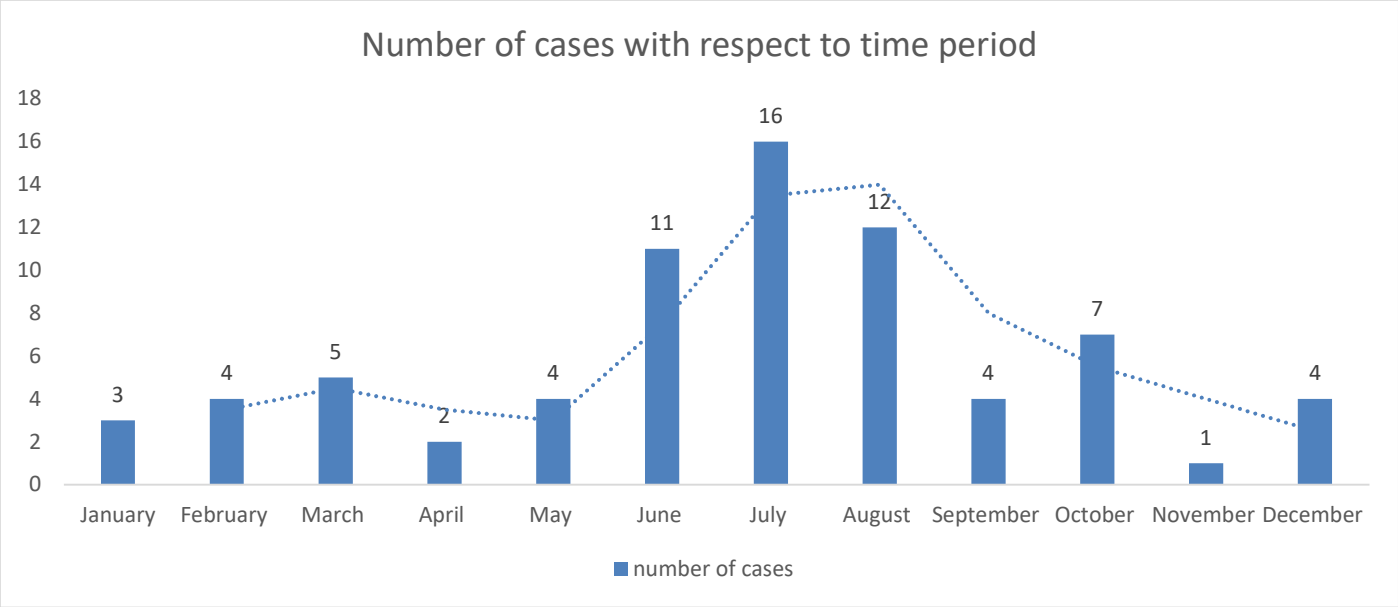

Figure 3: Syndromic presentation

Table 2: Source of infection	
Variable	N (%)
Sore throat	8 (11)
Pyoderma	4 (5.50)
URTI	4 (5.50)
LRTI	2 (2.70)
Skin and soft tissue infection	24 (32.90)
Sepsis/Bacteraemia	0
UTI	1 (1.40)
Acute gastroenteritis	2 (2.70)
No clinical evidence of infection	28 (38.40)

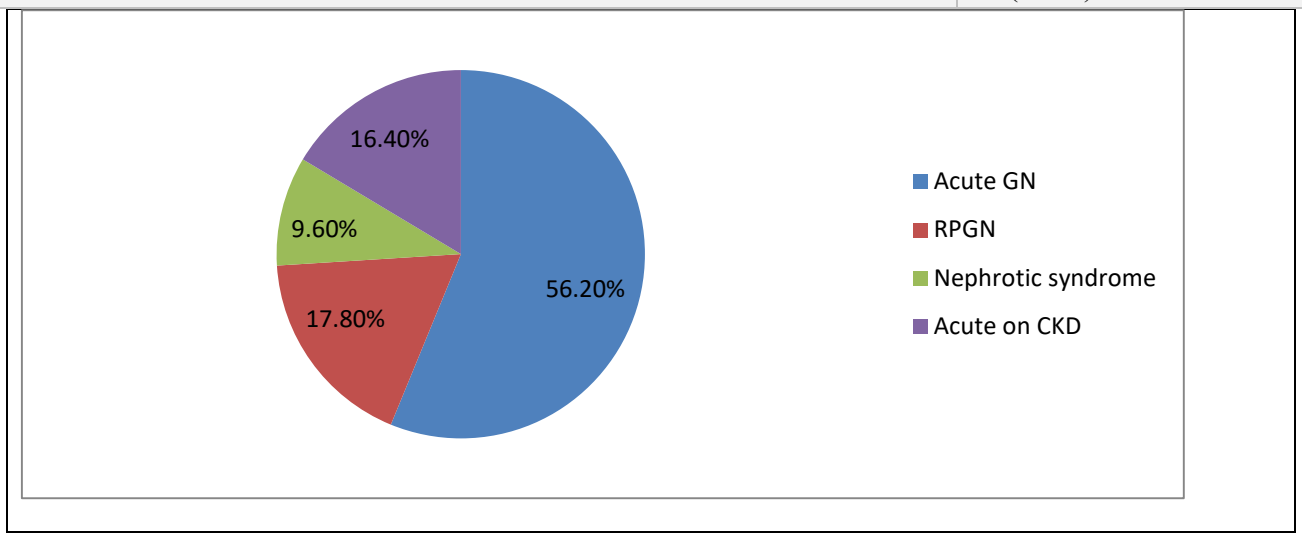

Table 3: Microbiology	
Microorganism	N (%)
Candida tropicalis	2 (2.70)
Klebsiella pneumonia	3 (4.10)
Pseudomonas aeruginosa	2(2.70)
MRSA	2(2.70)
None identified	64 (87.70)

Table 4: **Laboratory parameters**	
Laboratory parameters	Values
Creatinine at presentation (mg/dl)	3.10±2.5

Serum albumin (gm/dL) at presentation	3.08±0.475
EFGR (ml/min/1.73mt^2) at presentation	47.26±39.82
24-hour urine protein	3.14±1.4
Low complement level C3	57 (78.1)
Low complement level C4	13 (17.8)
Low C3+C4 level	26 (35.6%)
ASLO test positive	15 (20.5)
Need for renal biopsy	49 (68)

Histopathology:

Out of the 73 cases included in the final analysis, 49 patients fulfilled one of the indications for renal biopsy. The most common indication for biopsy was proteinuria>2gm/day both in adult as well as paediatric populations as illustrated in figure 4.

100% of the samples showed an endocapillary proliferative pattern, 97.9% showed a mesangial proliferative pattern, and 6.1% showed MPGN pattern. 80.8% had an exudative neutrophilic infiltration. Crescentic IRGN, which is characterized by more than 50% of glomeruli displaying crescents, was uncommon (8.61%). 75.5% of patients had interstitial cellular infiltration, and 63.2% had severe Interstitial edema. In 12% of cases, acute tubular damage was identified. The most common co-existing pathology was diabetic nephropathy seen in 18.36% patients as shown in Table 6

C3 was the universal immunological reactant with IgG being the most common immunoglobulin (69.4%) and IgM being the least common (4.1%). C3 was sole immune reactant in 22% of biopsies, while in 20% biopsies it was dominant by at least 2 grades. In 12.2 % biopsies, C1q was deposited, and it was consistently weaker than C3. 10% of biopsies had IgA codominant pattern and in 4% biopsies full house pattern was seen as shown in Table 7

Figure 4: Indications for renal biopsy

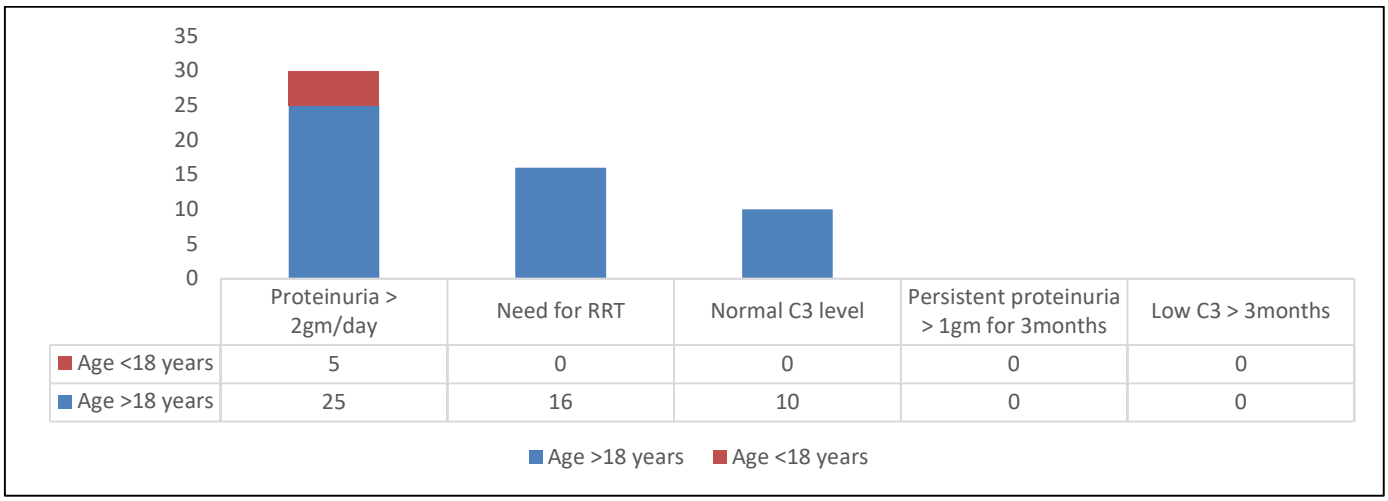

Table 6: **LM findings**		
Variable		Values
LM findings	Endocapillary proliferation	49 (100)
	Mesangial proliferation	48 (97.9)
	MPGN	3 (6.1)
	Crescentic IRGN (>50%)	4 (8.61)
	Crescents >20%	10 (20.4)
	Exudative neutrophil infiltration	9 (18.3)
	Capillary loop obliteration	33 (67.3)
	Lobular accentuation	0
	Interstitial inflammation	37 (75.5)
	Plasma cell infiltration	1 (2.04)
	Eosinophil infiltration	0
	Interstitial edema	31 (63.2)
	Acute tubular injury	6 (12)
	RBC casts	12 (24.4)
	Global glomerulosclerosis >20% / > 50%	2 (4.08)
	IFTA > 10%	22 (44.8)
Co-existing pathology	Diabetic nephropathy	9 (18.36)
	Nil	40 (81.63)

Table 7: **IF profile and patterns**		
Variable		Values
IF profile	C3	47 (95.9)
	Ig G	34 (69.4)
	Ig A	7 (14.3)
	Ig M	2 (4.1)
	C1q	6 (12.2)
IF pattern	Only C3	11 (22.4)
	C3>2+ dominant	10 (20.4)
	IgG/C3 co dominant	19 (38.7)

	IgG dominant	0 (0)
	IgA co-dominant	5 (10.20)
	Full house	2 (4)

Data on clinical outcomes and follow-up:

Total patients who recovered completely were 75.3%. HTN was persistent in 54.8% patients for more than 6 months and was more common in adult population and was clinically significant (p value < 0.001), proteinuria (>500mg) with normal renal functions was found in 27.4% for more than 6 months, patients who ended up with ESRD were 10 (3.7%) and 8 Out of 19 patients requiring RRT, continued on hemodialysis and all these patients were aged >50 years as shown in Table 8. Comparison of the patients who progressed to CKD with the patients who showed complete recovery, showed no significant characteristic differences as shown in Table 9.

Table 8: Follow up and clinical outcome of patients

Outcome	**All patients**	**<18 years**	**>18 years**	**P value**
Complete recovery	55 (75.3)	10	45	0.051
Persistent HTN >6 months	40 (54.8)	0	40	<0.001
Persistent proteinuria with normal renal functions > 6months	20 (27.4)	1	19	0.184
ESRD	10 (13.7)	0	10 (15.9)	0.175
RRT continued	8 (10.9)	0	8 (10.9)	0.002

Table 9: Comparison between patients who ended up as CKD and who had complete recovery

Comparative parameters	**Complete recovery**	**CKD (including ESRD)**	**P value**
Age >18 years	45	20	0.16
Requiring RRT	9	10	<0.001
Initial hypertension	50	20	0.578
Renal biopsy indicated	32	17	0.005
Proteinuria (>2gm/day)	21	11	0.344

The cohort was categorised into two subgroups: paediatric, defined as those under 18 years of age, and adults. The paediatric group exhibited less severe illness, typically presenting with acute nephritis and favourable clinical outcomes. AKI and peak creatinine levels were markedly reduced in the paediatric group and none of them underwent RRT compared to the adult group as shown in Table 10.

Table 10: Pediatric versus adult comparison

Parameter	Paediatric	Adult	P
No of cases	10	63	
Mean age, years (SD)	15.8±2.4	48.67±3.7	0.000
Male	8 (80%)	43 (68.3%)	0.452
Micro haematuria	6 (60%)	44 (69.8%)	0.534
Macro haematuria	2 (20%)	6 (9.5%)	0.325
AKI	4 (40%)	49 (77.8%)	0.013
Mean creatinine mg/dl (SD)	2.19±1.1	3.13±2.1	0.553
Low C3	10 (100%)	47 (74.6%)	0.071
Acute GN	10 (100)	31 (49.20)	0.128
RPGN	0	13 (20.63)	0.363
Nephrotic syndrome	0	7 (11.11)	0.065
Acute on CKD	0	12 (19.04)	0.564
Biopsy need	4(40)	45 (71.4)	0.175
Requiring RRT	0	19 (30.2)	0.043
CKD progression	0	20 (31.74)	0.202
ESRD	0	10 (15.9)	0.175

Age >40 years (p=0.001), alcohol intake (p=0.001), peak creatinine >1.5 mg/dl (p=0.001) and RRT requirement (p-0.001) were associated with failure to attain complete recovery and were identified as independent risk factors as shown in table 12.

Table 12: Risk factors predicting failure to achieve complete remission

Variable		Complete recovery		P value
		Yes	No	
Age	<40 years	25 (45.5%)	0	0.001
	>40 years	30 (54.5%)	18 (100)	
Alcohol	No	42 (76.4%)	6 (33.3%)	0.001

	Yes	13 (23.6%)	12 (66.7%)	
Peak creatinine	<1.5	24 (43.65)	0	0.001
	>1.5	31 (56.4%)	18 (100)	
RRT required	Yes	9 (16.4%)	10 (55.6%)	0.001
	No	46 (83.6%)	8 (44.4%)	

DISCUSSION:

Infection-related glomerulonephritis is an immune-mediated kidney damage resulting from prior or current infections, predominantly of bacterial origin. Historically, the majority of IRGN cases have been reported mostly in the pediatric population, typically following episodes of pyoderma or pharyngitis. Nonetheless, in the past thirty years, there has been increasing apprehension regarding the alarming changes in the epidemiology, microbiology, and final clinical consequences of the IRGN. [6]

In contemporary times, affluent nations have had a notable transformation in the prevalence of this GN, with a significant increase in the number of affected people, especially among the elderly and immunocompromised populations. Developing countries bear a significant burden of IRGN, despite a relatively low number of actual cases accessing healthcare facilities. The actual prevalence of IRGN is probably significantly more than reported in the literature, as epidemiological studies account solely for symptomatic patients, and it is established that subclinical IRGN occurs at least four times more frequently than clinically apparent disease.[14]

The present retrospective study was conducted at department of nephrology at a tertiary care center among 73 patients diagnosed with IGRN to assess the clinicopathological profile and outcomes of infection related glomerulonephritis. The mean age of the patients was 44 years which was similar as seen in most case series. [5,18] Number of male patients were more than female patients. This was similar to previous literature, where there is either a male dominance or equivalence between both sexes. [2,3,6,13] Males, however, had a higher risk for RPGN presentation and RRT need. [12] Most of the cases were seen in June to October months with peak cases in July which was different from most previous studies from south india where most of the cases were reported in September. [11,16]

In our series, majority of our patients exhibited acute nephritic syndrome, often characterised by the presence of haematuria, proteinuria, oedema, frequently accompanied by hypertension and a minor degree of renal impairment. Peripheral oedema was observed in 97.3% of patients, hypertension in 93.15%, and microhematuria in 68.5%, consistent with findings from earlier reported case studies. [3-5] Proteinuria of nephrotic range was infrequently seen in the past. [19] Nonetheless, nephrotic range proteinuria has been reported often in recent studies, with rates ranging from 13.8% to 60% in a handful of investigations. [13,15] We found that 24.65% of our patients had nephrotic range proteinuria. Recent Indian study results reveal an increasing prevalence of RRT need, ranging from 17.5% to 35.6%, [13,15,16] in contrast to previous findings.[12] In our study, 26% required RRT initiation at presentation.

Patients with IRGN may experience infections from multiple sources, including the upper respiratory system, skin, lungs, heart, urinary tract, oral cavity, bone, and deep-seated visceral or somatic abscesses.[1] The upper respiratory tract and skin are the most prevalent sites among them. In our investigation, the predominant sites of infection were skin and soft tissue infections followed by sore throat. Klebsiella was the most common organisms in our investigation, which was a

different finding from most previous studies.[4] Notwithstanding the comprehensive systematic screening for an infectious source, 87.7% of our patients exhibited no clinical signs of infection. This aligns with majority of other reported series. [13,16]

On renal biopsy, diffuse proliferative and exudative GN is the most prevalent finding in LM. [1] In our study, the most common LM finding was the typical endocapillary proliferative GN seen in 100% of the patients, 97.9% demonstrated a mesangial proliferative pattern, and 6.1% presented with membrano-proliferative glomerulonephritis. Crescentic IRGN, defined by over 50% of glomeruli exhibiting crescents, was infrequent (8.61%). These findings were similar to most of the previous studies. [1,4,5] 75.5% of patients exhibited interstitial cellular infiltration, whereas 63.2% presented with severe interstitial oedema. Acute tubular injury was found in 12% of patients while 44.8% cases had IFTA>10%. C3 dominant or codominant glomerular staining is most frequently observed in immunofluorescence (IF). It may exhibit distinct patterns, commonly referred to as the "starry sky pattern," "garland pattern," or "mesangial pattern," based on whether the capillary wall or mesangium is stained. In our study, we had a predominance of C3 deposits in dominant or codominant pattern seen in 95.9% cases. IgA deposits in a codominant pattern were seen in 14.3% cases.

Baldwin et al.[20] and Chugh et al.[21] documented long-term follow-ups of patients with PIGN for 60 months and 4.5 years, respectively. Irreversible renal disease, indicated by hypertension (42%), proteinuria (42%), diminished renal function (38%), glomerulosclerosis (10%), was documented in the former study, while persistent hypertension (15%), end-stage renal disease (1.9%), and chronic renal failure (3.8%) were noted in the latter study. In our study 75.3% had complete recovery, hypertension (HTN) persisted in 54.8% of cases for over six months, while proteinuria with normal renal function was observed in 27.4% for the same duration. 27.4% progressed to CKD while 15.06% patients remained dialysis dependent.

Age >40 years, alcohol intake, peak creatinine >1.5 mg/dl and RRT requirement were associated with failure to attain complete recovery and were identified as independent risk factors. Adults with IRGN do not always have a good prognosis in the long run. Therefore, it is important to frequently follow-up all patients, especially older patients and those with co-morbidities, for occurrence of CKD.

CONCLUSION

Acute nephritic syndrome is the typical presentation of IRGN, which is prevalent in underdeveloped nations. In adults and elderly patients, clinical diagnosis is frequently challenging since the infection may be chronic or its location may not be visible. IRGN may manifest as worsening of preexisting renal failure or as severe renal impairment necessitating dialysis. Renal biopsies are crucial for determining the underlying GN and evaluating prognosis; they should be considered early, particularly in individuals who have severe proteinuria, renal failure, or an initial need for RRT. Crescentic IRGN in biopsy and initial RRT demand may indicate a poor prognosis and increased risk of developing CKD.

Financial support and sponsorship: Nil

Conflict of interest: There are no conflicts of interest.

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