Bacterial Infection Related Glomerulonephritis in Patients with Diabetes Mellitus

John EE[1], Roy S[2], Karuppusami R[3], Raj SS[1], Johny J[1], Jose N[1], Eapen JJ[1], Thomas A[1], Yusuf S[1], Valson AT[1], David VJ[1], Varughese S[1], Alexander S[1]

[1]Department of Nephrology, [2]Department of Pathology, [3]Department of Biostatistics, Christian Medical College, Vellore

INTRODUCTION

Patients with underlying Diabetes Mellitus are prone to develop various infections, thus making them a unique cohort at risk of developing bacterial infection related glomerulonephritis (IRGN).

AIM

To determine the nature of infections, infecting organism, anti-bacterial susceptibility, renal histology, use of immunosuppressants, long-term renal outcomes and factors associated with progression to kidney failure in diabetic patients with biopsy proven IRGN.

METHODS

Total native kidney biopsies in adult diabetic patients between 2005-2021
N=1693

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Presumptive Bacterial-Infection Related Glomerulonephritis
N=140

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Definite Bacterial-Infection Related Glomerulonephritis (meeting at least 3/5 criteria)
N=129

→ Excluded (8)
-Inadequate kidney biopsy (6)
- Revision of diagnosis (2)

↓

Final Cohort
N=121

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- IRGN without Diabetic Kidney Disease **N=15 (12%)**
- Superimposed IRGN on Diabetic Kidney Disease **N=106 (88%)**
  - Class 1 DKD- 6 (5%)
  - Class 2 DKD- 42 (35%)
  - Class 3 DKD- 31 (26%)
  - Class 4 DKD- 27 (22%)

RESULTS

Table 1: Baseline Characteristics at Kidney Biopsy

Baseline Characteristics	Entire Cohort (N=121)
Sex (n, %)	
Men	83 (68.6)
Women	38 (31.4)
Age, years (mean ± SD)	53.1 ± 10.1
Hypertension (n, %)	111 (91.7)
Diabetes Mellitus	
Type of Diabetes Mellitus	
Type 1 DM	1 (0.8)
Type 2 DM	119 (98.3)
Gestational DM	1 (0.8)
Duration of diabetes, years [median (IQR)]	6 (2-12)
Microvascular complications (n, %)	
Diabetic retinopathy	41 (62.1)
Peripheral Neuropathy	24 (19.8)
Macrovascular complications (n, %)	
Coronary artery disease	15 (12.4)
Cerebrovascular accident	1 (0.8)
Peripheral vascular disease	8 (6.6)
HbA1c at biopsy, % (mean ± SD)	7.7 ± 1.8
Site of infection (n, %)	
Skin	47 (38.8)
Urinary tract infection	15 (12.4)
Upper respiratory tract	4 (3.3)
Lung	3 (2.5)
Causative organisms (n, %)	
Streptococcus pyogenes	22 (18.2)
Staphylococcus aureus	6 (4.9)
Gram-negative organism	21 (17.3)
Drug resistant organisms	24 (19.8)
Latency based classification	
Parainfectious GN	61 (50.4)
Postinfectious GN	25 (20.7)
Latent infectious GN	35 (28.9)
Latent period in postinfectious GN, days [median (IQR)]	17 (12-32.5)

Table 2: Baseline investigations at kidney biopsy

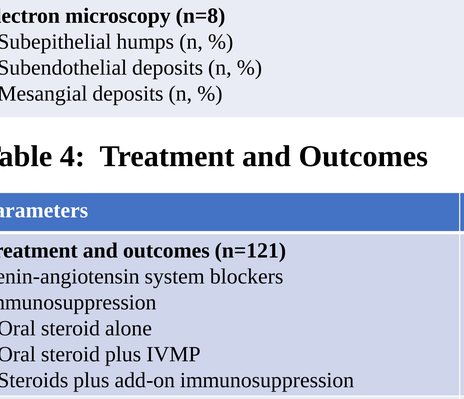
Baseline Investigations at kidney biopsy	Entire cohort (N=121)
Hemoglobin, g/dl (mean ± SD)	9.8 ± 2
Kidney function at biopsy	
Serum creatinine, mg/dL [median (IQR)]	5.2 (2.5-7.5)
eGFR CKD-EPI, ml/min/1.73 m² [median (IQR)]	10.8 (6.7-25.4)
Urine abnormalities (n, %)	
Nonvisible hematuria	104 (88.9)
Leucocyturia	72 (61.5)
Casts	57 (48.7)
24-hour urine protein, g/day [median (IQR)]	4.7 (2.5-7.7)
Serum albumin, g/dL (mean ± SD	2.9 ± 0.7
Serum complements, mg/dl (n, %)	
Low C3	90 (78.9)
Low C4	6 (5)
Serology (n, %)	
Elevated ASO	15 (22.4)
Elevated anti-DNase B	38 (58.5)

Table 3: Baseline Histopathological Parameters

Histopathological parameters	Entire cohort
Time to kidney biopsy from onset of GN, days [median (IQR)]	16 (10-32)
Light microscopy (N=121)	
Number of glomeruli (mean ± SD)	12.1 ± 4.8
Light microscopy pattern	
Mesangial proliferation	4 (3.3)
Focal exudative and endocapillary proliferation	16 (13.2)
Diffuse exudative and endocapillary proliferation	98 (81)
Membranoproliferative pattern	3 (2.5)
Crescents	32 (26.4)
>50% crescents	5 (4.1)
Acute tubular injury	71 (58.7)
Interstitial inflammation (focal, diffuse)	92. 23 (76, 19)
IFTA moderate to severe	48 (39.7)
Arterio(lo)sclerosis	111 (91.7)
Immunofluorescence staining (N=120)	
IF pattern (n, %)	
Starry sky	53 (43.8)
Garland	51 (42.1)
Mesangial	17 (14)
Isolated C3 staining (n, %)	66 (54.5)
IgA dominant GN (n, %)	9 (7.4)
Electron microscopy (n=8)	
Subepithelial humps (n, %)	7 (87.5)
Subendothelial deposits (n, %)	7 (87.5)
Mesangial deposits (n, %)	5 (62.5)

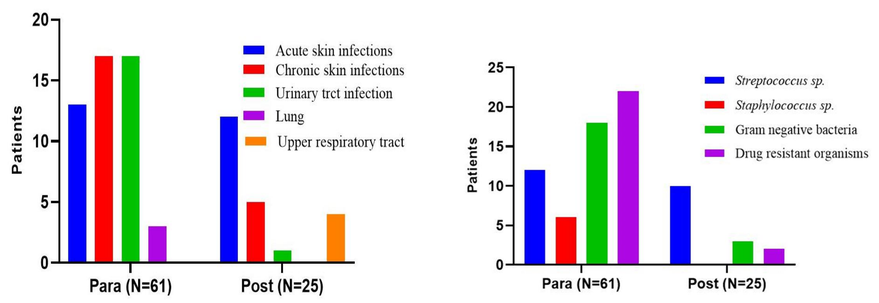
Table 4: Treatment and Outcomes

Parameters	Entire Cohort
Treatment and outcomes (n=121)	
Renin-angiotensin system blockers	34 (21.1)
Immunosuppression	86 (71.1)
Oral steroid alone	65 (53.7)
Oral steroid plus IVMP	21 (17.4)
Steroids plus add-on immunosuppression	6 (5)
Outcomes at last follow up (n=90)	
>3 months of follow-up (n, %)	90 (74.3)
Follow-up duration, months [median (IQR)]	6 (3-22.5)
Kidney outcomes (n, %)	
Remission	34 (37.8)
Stabilization	8 (8.9)
Worsening	2 (2.2)
Kidney failure	46 (51.1)
Proteinuria outcomes (n, %)	
Complete remission	24 (45.3)
Partial remission	13 (24.5)
No remission	16 (30.2)
Immunosuppression related adverse events	
Steroid induced dysglycemia	9 (14.8)
Steroid induced cataract	0
Immunosuppression-related infections	16 (26.2)
Death	8 (8.9)

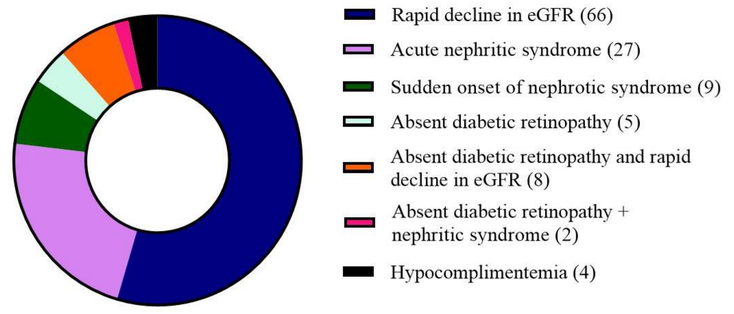


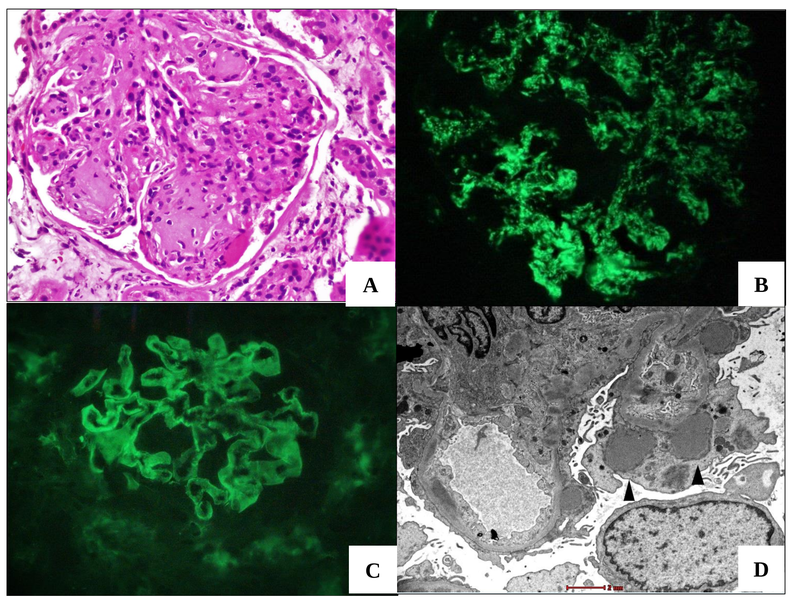
Severity of Diabetic Kidney Disease

Site of infection and infectious agent (Latency based classification)



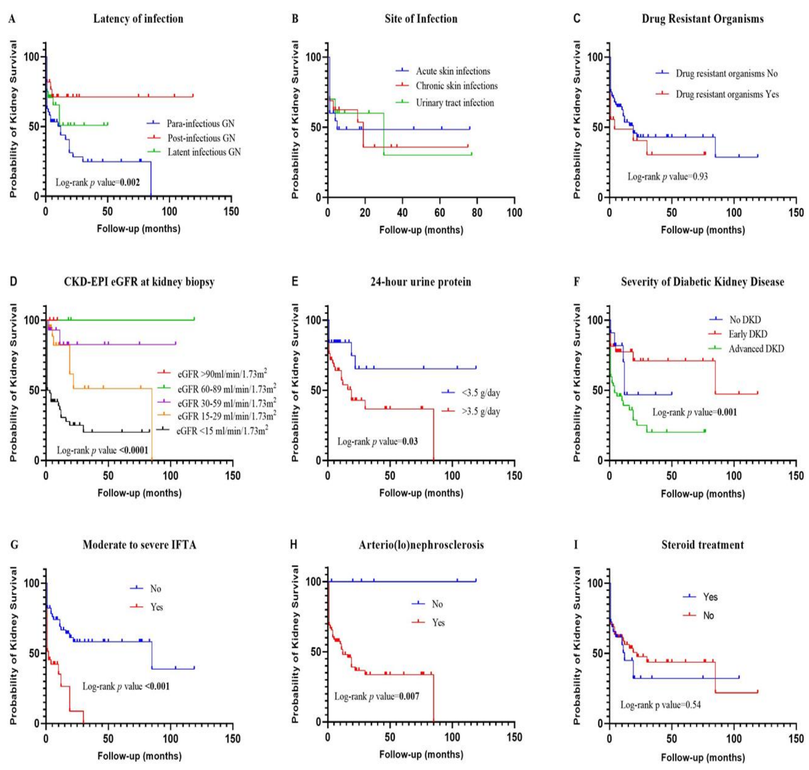
Indication for Kidney Biopsy

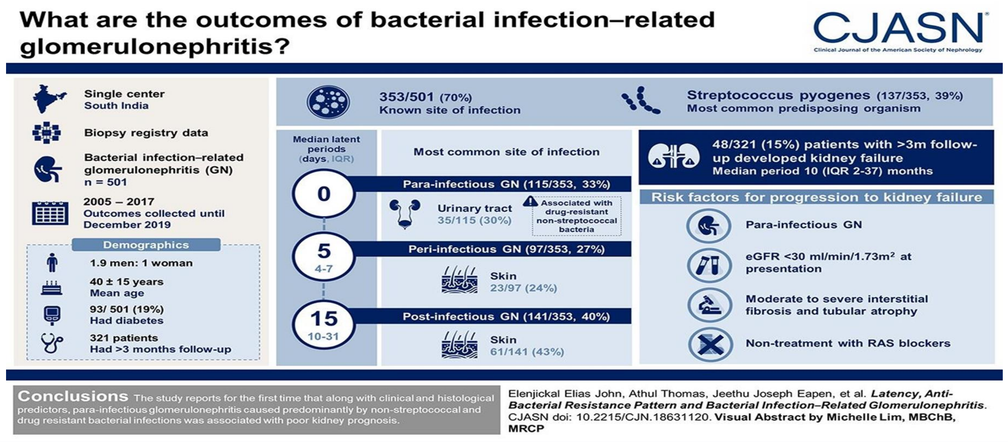




A. Light Microscopy-**Superimposed IRGN on Diabetic glomerulosclerosis**
B. Immunofluorescence Microscopy- **'Starry sky pattern'**
C. Immunofluorescence Microscopy- **'Garland Pattern'**
D. Electron Microscopy- **'Sub-epithelial humps'**

Characteristics associated with progression to kidney failure





CONCLUSIONS

- **Para-infectious glomerulonephritis** characterized by an ongoing infection at onset of GN was seen in 61/121 (50%) patients.
- The most common sites of infection were skin [47/121 (39%)] and urinary tract [15/90 (12%)]. UTI and lung infections were more common in para-infectious group, whereas all cases of upper respiratory tract infections occurred in the post-infectious group.
- The most common isolated infectious organism was Streptococcus Pyogenes (22/121, 18%). Gram-negative and drug resistant organisms were isolated in 21/121 (17%) and 24/121 (20%) cases.
- Staphylococcal, gram-negative and multi-drug resistant infections occurred more commonly in the parainfectious group.
- Short-course oral steroid was given to 86/121 (71%) patients. 16/59 (26 %) patients treated with immunosuppressants developed infections over the follow-up period, majority belonging to para-infectious group (11/16, 69%).
- **eGFR <30 ml/min/1.73m² at presentation**, **nephrotic range proteinuria, para-infectious GN, advanced DKD** and **moderate to severe interstitial fibrosis and tubular atrophy** on kidney biopsy were the significant predictors of kidney failure by Cox-regression hazard model.

References

1. John EE, Thomas A, Eapen J, Yusuf S, Roy S, Valson A, David V, Varughese S, Alexander S: Latency, Anti-Bacterial Resistance Pattern, and Bacterial Infection-Related Glomerulonephritis. Clin J Am Soc Nephrol 2021
2. Nast CC: Infection-related glomerulonephritis: changing demographics and outcomes. Adv Chronic Kidney Dis 19: 68–75, 2012