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Research Article

Preliminary Investigation of Poly-IgA as a Biomarker for Recurrence Risk of IgA Nephropathy after Kidney Transplantation: A Case Study

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Abstract

Background and objectives: A serological biomarker, polymeric IgA immune complex (Poly-IgA), was previously introduced for IgA nephropathy (IgAN). In this preliminary study, circulating Poly-IgA was investigated for patients after kidney transplantation, and a case study with provisional data suggests that Poly-IgA may serve as a potential biomarker for recurrence risk of IgAN after kidney transplantation.

Methods: Poly-IgA was tested using plasma samples from a cohort of kidney transplant recipients (KT) and healthy controls (HC). Descriptive statistics of Poly-IgA results were analyzed. Summary statistics were compared between KT and HC. In a rare case, an IgAN patient with 2-year transplantation was tested to have very high Poly-IgA concentration and was then confirmed to be a recurrent IgAN via biopsy. Time course analysis of Poly-IgA and traditional clinical metrics was performed for the period from two months before the biopsy to about 6 months after diagnosis of the recurrence and telitacicept treatment.

Results: On average, Poly-IgA levels in kidney transplant recipients were lower than those in healthy controls. Poly-IgA levels did not differ significantly between post-transplant IgAN and non-IgAN patients, and Poly-IgA was independent of age and time since transplantation. The case study demonstrated that Poly-IgA may be an easy-to-measure, reliable, and leading indicator for assessing recurrence risk of post-transplant IgAN and monitoring disease activity.

Conclusions: Poly-IgA levels are generally lower in kidney transplant recipients than in healthy controls, with no significant difference between IgAN and non-IgAN patients, and are independent of age and post-transplant follow-up time. A preliminary case study supports the hypothesis that Poly-IgA may be a leading indicator of recurrence risk in post-transplant IgAN patients. Larger prospective studies are needed to validate this hypothesis.

Abbreviations ESKD: End stage kidney disease; IgA: Immunoglobulin A; Poly-IgA: Poly- meric IgA immune complex; IgAN: IgA nephropathy; Gd-IgA1: Galactose-deficient IgA1; KT: Kidney transplantation group; HC: Healthy control group; CI: confidence interval.

Keywords: iga nephropathy; iga immune-complex; recurrence risk after kidney transplanta- tion; cd89; poly-iga

1.Introduction

Immunoglobulin A (IgA) nephropathy (IgAN) is a common kidney disease worldwide, accounting for approximately 40% of all biopsy-diagnosed kidney diseases in China [1].

Up to 40% of patients with IgAN develop end-stage kidney disease (ESKD) during their lifetime, requiring either kidney transplantation or dialysis; kidney transplantation remains the optimal treatment for ESKD. Nevertheless, the 10-year incidence of allograft failure due to recurrent IgAN exceeds 10%, and current recurrence diagnosis relies on hematuria, proteinuria, and biopsy findings that are inconsistent and delayed [2, 3]. Accurate and timely diagnosis of post-transplant recurrence remains an unmet clinical need, and serological biomarkers for post-transplant recurrence risk are highly desirable.

Based on the widely accepted multi-hit theory [4], galactose-deficient IgA1 (Gd-IgA1), IgG anti-Gd-IgA1 antibodies, and soluble CD89 have been investigated as recurrence biomarkers [5, 6, 7, 8]. Recently, circulating polymeric IgA immune complex (Poly-IgA) has been proposed as a broader biomarker for IgAN, and an assay using recombinant CD89 has been developed [9, 10]. Furthermore, Poly-IgA shows superior sensitivity for monitoring treatment responses to telitacicept [11] or targeted-release budesonide [12] in IgAN. This study hypothesizes that Poly-IgA may act as a leading indicator of IgAN recurrence risk after kidney transplantation, supported by a case study.

2 Materials and Methods

Sample Enrollment and Testing Twenty-nine kidney transplant recipients (KT group) at Xuanwu Hospital were enrolled with written informed consent for Poly-IgA testing; 11 had biopsy-proven IgAN before transplantation. Twenty-eight age-matched healthy volunteers were enrolled as healthy controls (HC). Biopsy pathology reports and routine clinical data were col- lected. The study was approved by the local ethics committee (approval number: KS2023244). Blood samples (2–5 mL) were collected in EDTA tubes, packed on ice, and shipped to the R&D laboratory of Shenzhen Luwei Biotechnology Co., Ltd. where Poly-IgA was measured using the IgA Nephropathy ImmunoActivity Test Kit (ELISA) manufactured by the company (https://en.biomanifold.com/product-1/IgAN/). The ELISA kit uses recombinant CD89 as the capture molecule to quantify Poly-IgA in serum or plasma.

Data Analysis Descriptive statistics were calculated for Poly-IgA and clinical markers. The Grubbs test was used for outlier detection, the Shapiro–Wilk test for normality, and the Hartley (F-max) test and t-test to evaluate differences by disease type, age group, and post-transplant duration. Summary statistics were compared between KT and HC groups. One outlier with extremely high Poly-IgA was identified; the patient was diagnosed with recurrent IgAN by biopsy 2 weeks later. Monthly follow-up data from 2 months before outlier detection to 6 months after recurrence diagnosis were assembled and analyzed. Time-course changes in Poly-IgA and conventional clinical markers were compared. All statistical analyses and plotting were performed using in-house R scripts.

3 Results

Descriptive Statistics Of the 29 KT patients analyzed, 11 (38%) had pre-transplant IgAN and 18 had non-IgAN kidney disease; only 3 were female. Mean age was 42 years (range: 30–67 years). Mean post-transplant follow-up (3 missing values) was 2.67 years (median: 2.5 years; range: 0.5–6 years). The summary statistics of Poly-IgA are show in Table 1.

Group	Size	Mean	Median	Range
KT group (all patients)	29	44.25	41.95	15.99–108.75
HC group	28	52.66	52.90	27.71–79.34
KT-IgAN subgroup	11	48.48	46.33	21.45–108.75
KT-non-IgAN subgroup	18	41.27	41.68	15.99–75.43

Table 1: Summary of Poly-IgA levels (U/mL) in study groups

Analysis of Poly-IgA and identification of a recurrent IgAN case Grubbs test identified the maximum value (108.75 U/mL) as an outlier ($G = 3.2075$, $U = 0.6194$, $p = 0.0053$). After removing the outlier, Shapiro–Wilk test confirmed normality ($W = 0.9689$, $p = 0.5514 > 0.05$). Patients were stratified by age (< 40 vs. ≥ 40 years) and post-transplant duration (< 3 vs. ≥ 3 years). Hartley tests showed homogeneous variance across disease, age, and duration subgroups (F-max < critical value). T-tests revealed no significant differences in Poly-IgA levels between any subgroups ($p > 0.05$ for all; Figure 1). After excluding the outlier, the KT group had significantly lower Poly-IgA than the HC group ($p = 0.0108 \leq 0.05$), with a ∼20% median reduction.

Analysis of the Recurrent IgAN Case The outlier (108.75 U/mL) was measured on July 25, 2025, in a male patient 2 years post-transplant with biopsy-proven pre-transplant IgAN and ESKD. On May 26, 2025, the patient tested positive for John Cunningham (JC) virus (viral load∼1 × 109 copies/mL; < 1000 copies/mL = negative). On July 25, 2025:

- Urine red blood cell (RBC) count = 51/μL (above normal range: 0–25/μL)
- Poly-IgA = 108.75 U/mL (well above the kit cutoff of 75.6 U/mL)
- eGFR = 59 mL/min/1.73m² (declined from 65 mL/min/1.73m² 1 month prior; below the normal threshold of 60 mL/min/1.73m²)

Biopsy on August 8, 2025, confirmed recurrent IgAN. Immunostaining showed strong mesangial IgA (+++) and C3 (+++) deposition (Figure 3), with IgM (+) and C1q (–). IHC staining showed scattered CD3+ T lymphocytes in the renal interstitium (Figure 4), with minimal CD4+/CD8+/CD20+/CD38+ cells; EBV and CMV were negative, excluding acute infection, lupus, and lymphoma. HLA testing was negative, ruling out acute rejection despite maintenance tacrolimus. After diagnosis, the patient received telitacicept 80 mg weekly for 3 months, then every 2 weeks starting November 2025.Time-course analysis (Figure 2):

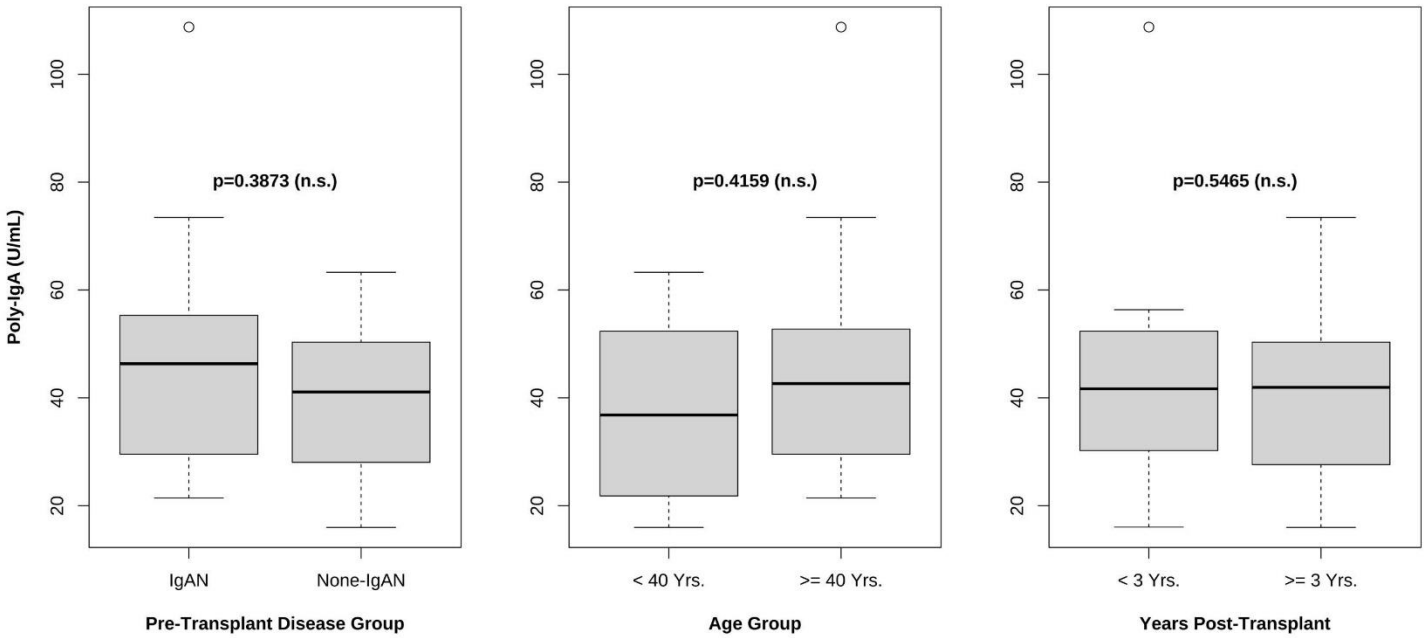

Figure 1: Box plots of Poly-IgA concentrations by pre-transplant disease type (IgAN vs. non-IgAN), age group (< 40 vs. ≥ 40 years), and post-transplant duration (< 3 vs. ≥ 3 years). T-tests show p > 0.05 for all comparisons; Poly-IgA distribution is unaffected by disease type, age, or post-transplant time (n.s. = not significant).

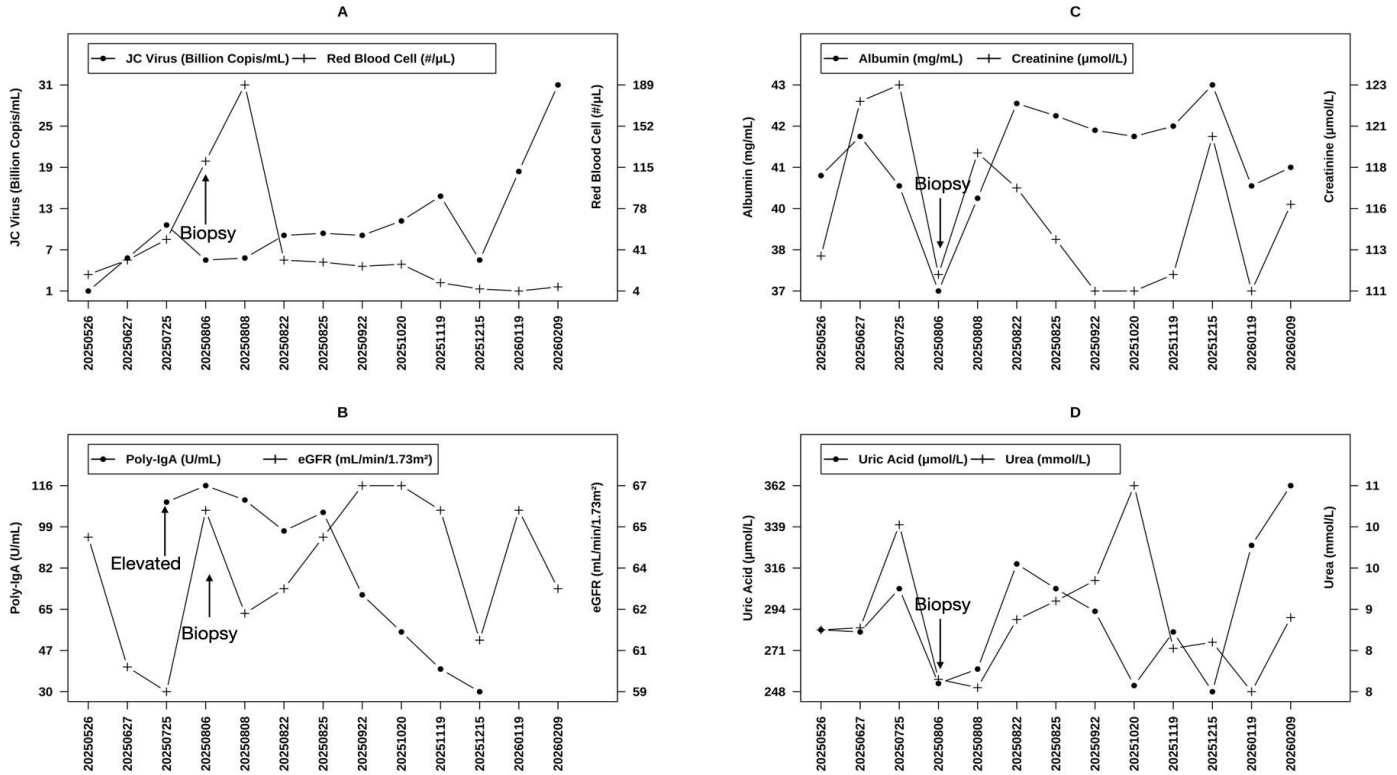

Figure 2: Time courses of Poly-IgA and other clinical metrics for a recurrent IgAN patient after 2 years of kidney transplantation (Arrows: Poly-IgA outlier test date and biopsy date; Magnification bars: left or right y-axis markers). A. JC virus load (left; < 1000 = negative) and red blood cell counts (right; normal: 0 - 25 #/μL). B. Poly-IgA (left; normal: 15.63 - 75.60 U/mL) and eGFR (right; normal: ≥ 60 mL/min/1.73m2). C. Albumin (left; normal: 35 - 55 mg/mL) and creatinine (right; normal range: 18 - 104 μmol/L). D. Uric acid (left; normal: 155- 428 μmol/L) and Urea (right; normal range: 1.7 - 8.3 mmol/L).

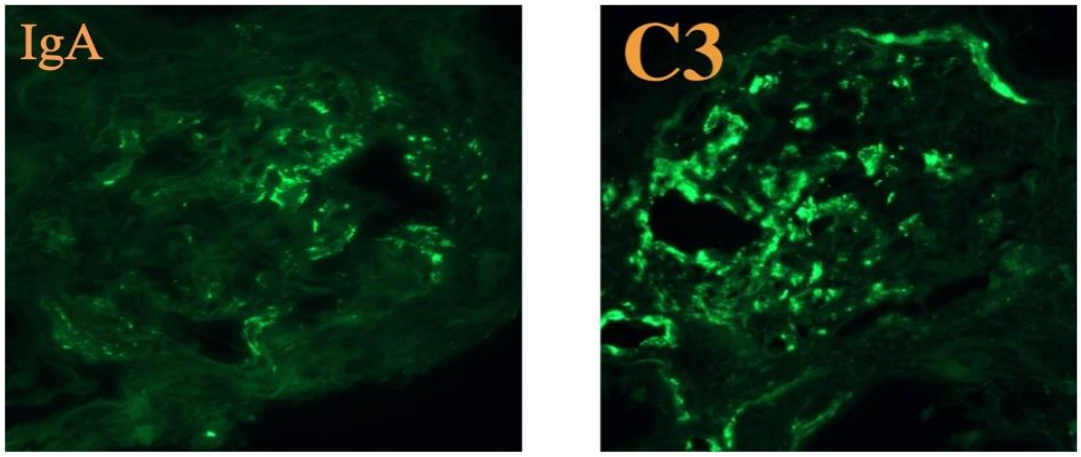

Figure 3: IgA and C3 immunostaining of renal biopsy tissue from the recurrent IgAN patient. Left: IgA shows punctate mesangial deposition; right: strong C3 staining. Pathology report: IgA (+++), C3 (+++), IgM (+), C1q (–) (IgM/C1q images not shown).

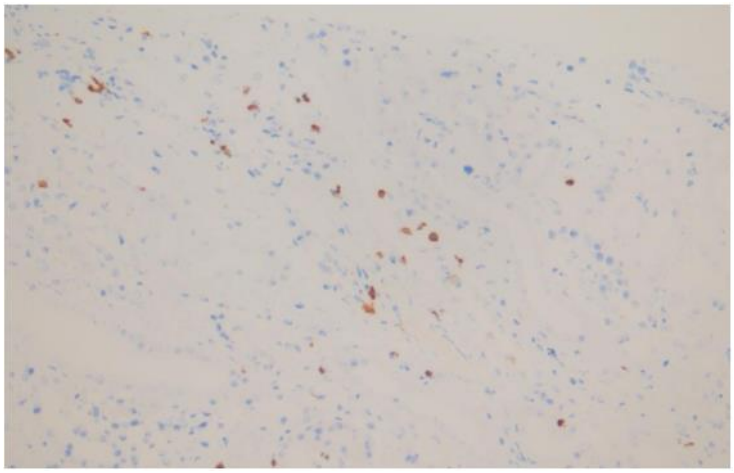

Figure 4: IHC stains of CD3. CD3+ (brown) T-lymphocytes scattered in the renal interstitium.)

- Plot A: Urine RBC rose before biopsy and declined slowly after telitacicept; JC viral load trended upward.
- Plot B: Poly-IgA decreased rapidly after treatment, normalized within ∼1 month, and fell by 72% at 4 months; eGFR stabilized above 60 mL/min/1.73m^2.
- Plot C: Albumin remained normal; creatinine was mildly elevated (111–123 µmol/L; nor- mal: 18–104 µmol/L).
- Plot D: Uric acid was normal; urea was occasionally elevated.

Poly-IgA peaked on July 25, 2 weeks before urine RBC peaked (August 8). Both markers nor- malized by August 22 (2 weeks post-telitacicept), indicating treatment response. Other markers (albumin, creatinine, urea, uric acid) showed no meaningful changes, and eGFR did not im- prove or deteriorate markedly. This case supports Poly-IgA as a reliable early indicator of post-transplant IgAN recurrence.

Validation of Poly-IgA Cutoff for Post-transplant IgAN Recurrence Risk Cutoff values were defined as the 95th percentile with 90% confidence interval (CI):

- KT group: 95th percentile = 74.63 U/mL (90% CI: 53.84–86.83)
- HC group: 95th percentile = 75.16 U/mL (90% CI: 72.34–79.69)

The kit's diagnostic cutoff (75.60 U/mL) differs by < 2% from both 95th percentiles, supporting its use as a threshold for IgA immune pathway activation in kidney transplant recipients. The index case (108.75 U/mL) was well above this cutoff, clearly indicating immune activation and recurrence risk.

Limitations: Sample sizes were small due to limited patient availability. Larger clinical studies are needed to validate these findings and confirm Poly-IgA as a biomarker for post-transplant IgAN recurrence risk.

Data availability: Data are available upon reasonable request.

4 Discussion

Since IgAN pathogenesis is not fully elucidated, the mechanisms of post-transplant IgAN recurrence are also unclear. Biopsy remains the gold standard for recurrence diagnosis, but 18% of biopsy-proven recurrences are asymptomatic [13]. Serological biomarkers for post-transplant IgAN recurrence are therefore an unmet clinical need. IgAN patients have higher transplantation rates than other ESKD patients, and IgAN is the leading cause of allograft failure due to recurrence. Recurrence risk factors include: firstly, the recipient with higher initial IgA level, young age at transplant, rapid progression to ESKD, and higher proteinuria level; secondly, the living donor, the donor with zero HLA mismatched, and specific HLA types; lastly, the duration post-transplant and whether consistently use of Immunosuppression [2]. Previous studies iden- tified young age at diagnosis, rapid progression to ESKD, and glomerular cellular crescents as strong recurrence predictors [14, 15]. Early post-transplant serum IgA may predict recurrence [16]. Based on the multi-hit theory, Gd-IgA1, anti-Gd-IgA1 IgG, and soluble CD89 complexes have been widely studied; high pre-transplant Gd-IgA1 and IgA-IgG, and low

soluble CD89-IgA, correlate with recurrence [6, 7, 8]. Biopsy C4d staining is strongly linked to graft loss in re- current IgAN [17], and intra-renal complement transcripts are upregulated in failing allografts [18]. Pre-transplant TNFSF13 levels predict recurrence in living-donor transplant recipients [19]. Unlike Gd-IgA1, Poly-IgA includes Gd-IgA1-IgG complexes and other IgA complex subtypes, covering Gd-IgA1-negative IgAN patients. Renal biopsy shows diverse deposited Poly-IgA com- plexes (IgA1/IgA2 [20], IgA-IgG, IgA-IgM, IgA-C3, etc.). CD89-captured Poly-IgA is enriched in IgA-AMBP, IgA-TGFBI, and IgA-TF complexes associated with IgAN [10]. If validated, Poly-IgA may be more sensitive than Gd-IgA1 for post-transplant recurrence. Large prospective trials are required to confirm this hypothesis.

5 Conclusions

Poly-IgA levels do not differ between post-transplant IgAN and non-IgAN patients and are stable across age and post-transplant follow-up duration. Although median Poly-IgA is ~20% lower in transplant recipients than in healthy controls (statistically significant), the 95th percentiles are comparable between groups, supporting the kit cutoff of 75.60 U/mL for transplant recipients. Elevated Poly-IgA above this cutoff may signal impending recurrence. This case study supports the hypothesis that Poly-IgA is a leading serological biomarker for recurrence risk in post-transplant IgAN patients. It also shows potential for monitoring disease activity, treatment response, and therapeutic adjustments. Larger prospective clinical trials are needed to confirm these findings.

6 Declaration

Conflict of Interest: Aibing Rao is a co-founder of Shenzhen Luwei Biotechnology Co., Ltd., Shenzhen, China. All other authors declare no conflicts of interest.

Ethics Approval This study was approved by the Ethics Committee of Xuanwu Hospital (approval number: KS2023244).

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