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Tissue-Level Identification of Aberrantly Glycosylated IgA1: Implications for Renal Disease Classification and Clinical Outcomes

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Abstract

Background: Galactose-deficient immunoglobulin A1 (Gd-IgA1) is a central component of the immunopathological mechanisms underlying IgA nephropathy (IgAN). KM55, a monoclonal antibody directed against Gd-IgA1, offers a tissue-based approach to identifying abnormal IgA1 deposition. However, the diagnostic accuracy and clinical relevance of its immunohistochemical expression have not been fully established. This study investigated the diagnostic performance of KM55 staining and its relationship with histological findings and subsequent renal deterioration.

Methods: A retrospective evaluation was performed on 114 native kidney biopsies exhibiting mesangial IgA immunofluorescence of at least 1+. Seventy-five cases were classified as IgAN and 39 as non-IgAN glomerular disorders. Mesangial KM55 immunoreactivity was graded from 0 to 4+. Clinical characteristics, Oxford MEST-C parameters, and renal outcomes were assessed. Prognostic associations were examined using Kaplan–Meier analysis and Cox proportional hazards regression.

Results: KM55 staining was significantly more intense in IgAN than in non-IgAN specimens (median score, 3 versus 1; p less than .001). The diagnostic area under the receiver operating characteristic curve was 0.907, with an optimal threshold of 2+. Among patients with IgAN, those with staining scores of 3+ or 4+ demonstrated higher serum creatinine, blood urea nitrogen, proteinuria, and diastolic blood pressure, together with reduced eGFR and serum albumin. Mesangial hypercellularity was also more frequent in this subgroup. Univariate survival analysis demonstrated increased risks of end-stage renal disease, CKD stage 4, and substantial eGFR reduction. However, KM55 staining did not retain independent statistical significance after adjustment for histological variables, whereas tubular atrophy and interstitial fibrosis remained independently associated with renal deterioration.

Conclusion: Mesangial KM55 immunoreactivity may assist in differentiating IgAN from other IgA-containing glomerular disorders and provides additional information about disease severity. Its prognostic contribution requires confirmation through larger studies and standardized quantitative assessment.

Keywords: IgA Nephropathy; Galactose-Deficient IgA1; Immunohistochemistry; KM55 Monoclonal Antibody; Mesangial Deposition; Oxford Classification; Renal Prognosis; Glomerulonephritis.

INTRODUCTION

IgA nephropathy (IgAN) represents one of the most frequently encountered primary glomerular disorders worldwide. Its clinical presentation varies considerably, extending from isolated urinary abnormalities to progressive impairment of renal function and eventual kidney failure. Long-term observational studies indicate that approximately 30%–40% of affected adults may develop advanced renal insufficiency over two to three decades [1]. This variation in disease progression has encouraged continued investigation into the immunological and histological factors associated with renal injury.

The development of IgAN is closely associated with abnormalities in the O-glycosylation of immunoglobulin A1 (IgA1). Under physiological conditions, galactose is attached to N-acetylgalactosamine residues within the hinge region of IgA1. In affected individuals, incomplete galactosylation produces galactose-deficient IgA1 (Gd-IgA1), which can interact with circulating antiglycan antibodies. The resulting immune complexes accumulate within the glomerular mesangium, promoting inflammatory signaling, mesangial proliferation, complement activation, and extracellular matrix production [2].

The currently accepted pathogenic framework describes several interconnected events involving increased Gd-IgA1 production, autoantibody formation, circulating immune-complex generation, and subsequent glomerular deposition. These mechanisms provide a biological explanation for the relationship between abnormal IgA1 glycosylation and progressive glomerular injury [3]. Earlier investigations assessed Gd-IgA1 using lectin-based assays and mass spectrometry. Although informative, these approaches have practical limitations involving analytical consistency, technical requirements, and reproducibility. The introduction of the KM55 monoclonal antibody provided an alternative method for identifying Gd-IgA1 through a lectin-independent approach [4]. Its application in enzyme-linked immunosorbent assays has facilitated the measurement of circulating Gd-IgA1, while tissue-based immunohistochemistry has enabled direct assessment of glomerular deposition [5].

Previous investigations demonstrated increased KM55 expression in IgAN specimens compared with several other glomerular disorders. Nevertheless, differences in staining methodology, interpretation, and grading have complicated comparisons between studies. The diagnostic value of tissue staining also requires careful assessment because Gd-IgA1 immunoreactivity may occur in selected secondary IgA-associated conditions [6]. Renal biopsy remains fundamental to the diagnosis and classification of IgAN. The Oxford MEST-C system provides standardized assessment of mesangial hypercellularity, endocapillary proliferation, segmental sclerosis, tubular atrophy/interstitial fibrosis, and crescent formation. These parameters contribute to the evaluation of histological disease activity and chronic damage [7]. Clinical risk assessment additionally incorporates renal function, proteinuria, and blood pressure, as reflected in established clinical practice recommendations [8].

Although circulating Gd-IgA1 concentrations have been investigated in relation to renal deterioration, the significance of mesangial Gd-IgA1 deposition detected directly in biopsy tissue remains less clearly defined. A tissue-based assessment could provide information about the distribution and intensity of abnormal IgA1 deposition that cannot necessarily be obtained from serum measurements alone. Accordingly, the present investigation evaluated KM55 immunohistochemical expression in native kidney biopsies with mesangial IgA positivity. The study compared staining intensity between IgAN and non-IgAN disorders, examined its association with clinical and pathological characteristics, and assessed its relationship with subsequent renal outcomes. A subgroup analysis of COVID-19-associated IgAN was also performed.

MATERIALS AND METHODS

Study Population and Case Selection

This retrospective investigation included 114 patients who underwent native kidney biopsy at Severance Hospital, Seoul, South Korea, between January 2010 and June 2024.

Eligibility required:

1. More than three viable glomeruli per tissue section.
2. Mesangial IgA immunofluorescence intensity of at least 1+.
3. No previous kidney transplantation.

IgA immunofluorescence was classified as negative (0), trace (0.5+), mild (1+), moderate (2+), or strong (3+). Seventy-five cases fulfilled the diagnostic criteria for IgAN. The remaining 39 specimens were classified as non-IgAN glomerular diseases. The IgAN diagnosis was supported by dominant or codominant mesangial IgA staining, together with mesangial electron-dense deposits when glomeruli were available for electron microscopy. In cases without demonstrable electron-dense deposits, C3 immunofluorescence of at least 1+ was required. Systemic lupus nephritis was excluded using the established 2019

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EULAR/ACR classification criteria [9]. Nine patients whose clinical manifestations developed within 50 days of COVID-19 infection or vaccination were classified as COVID-19-associated IgAN.

The non-IgAN group consisted of 27 lupus nephritis cases, three post-infectious glomerulonephritis cases, two pauci-immune crescentic glomerulonephritis cases, and one case each of FSGS, IgA-dominant infection-related glomerulonephritis, IgM nephropathy, immune complex-associated crescentic glomerulonephritis, membranous nephropathy, membranoproliferative glomerulonephritis, and endocarditis-associated immune complex-mediated glomerulonephritis.

Histopathological Assessment

Renal biopsy specimens were processed using routine formalin-fixed, paraffin-embedded techniques. Sections underwent hematoxylin and eosin, periodic acid-Schiff, periodic acid methenamine silver, and acid fuchsin orange G staining. Immunofluorescence examination included IgG, IgA, IgM, C3, C4, C1q, fibrinogen, kappa, and lambda light chains. The Oxford classification was applied to all IgAN specimens. The histological components were categorized as follows:

- **M:** M0 or M1, according to the proportion of glomeruli exhibiting mesangial hypercellularity.
- **E:** E0 or E1, based on the presence of endocapillary hypercellularity.
- **S:** S0 or S1, according to the presence of segmental sclerosis or tuft adhesion.
- **T:** T0, T1, or T2, reflecting increasing degrees of tubular atrophy and interstitial fibrosis.
- **C:** C0, C1, or C2, according to the proportion of glomeruli containing crescents.

The Haas classification was also recorded, encompassing grades I–V. Electron microscopy findings were reviewed in all available specimens to determine the presence and distribution of mesangial electron-dense deposits.

KM55 Immunohistochemical Staining

Immunohistochemical staining was performed using an automated BOND-III platform (Leica Biosystems, Germany). Paraffin sections measuring 3 μm were dewaxed and subjected to heat-induced epitope retrieval using BOND Epitope Retrieval Solution 2 for 20 minutes. Protease 1 was subsequently applied at 0.38 mg/mL for 30 minutes (Figure 1).

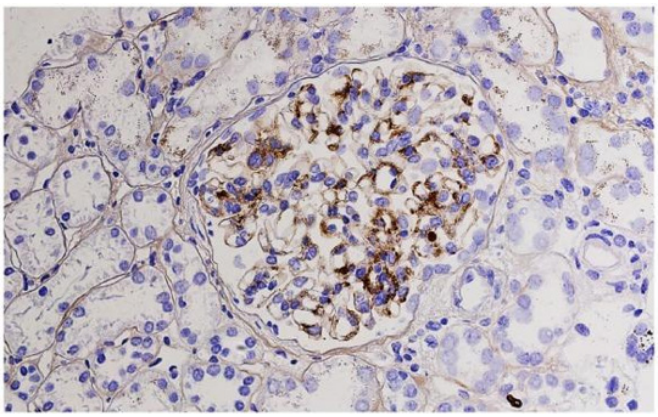


Figure 1: Representative mesangial KM55 immunohistochemical staining grades.

The KM55 primary antibody, a rat monoclonal antibody against human Gd-IgA1 (Immuno-Biological Laboratories, Japan), was used at a concentration of 10 μg/mL for 15 minutes. A conjugated goat anti-rat IgG secondary antibody was applied for 15 minutes. Signal visualization was performed using the Bond Polymer Refine Detection Kit, with 3,3′-diaminobenzidine as the chromogen and hematoxylin counterstaining. Positive controls consisted of previously confirmed IgAN specimens, whereas nephrectomy tissues without medical renal disease served as negative controls (Table 1).

Score	Staining intensity
0	No detectable staining
1+	Faint staining
2+	Weak staining
3+	Moderate staining
4+	Strong staining

Table 1: Mesangial staining was evaluated according to a five-grade system.

Clinical Variables and Outcome Assessment

Clinical information was obtained from electronic medical records. Recorded parameters included age, sex, presenting manifestations, blood pressure, serum creatinine, serum albumin, blood urea nitrogen (BUN), estimated glomerular filtration rate (eGFR), urine protein-to-creatinine ratio (UPCR), uric acid, and hematological measurements. Serum C3, C4, and IgA concentrations were collected when available. eGFR was calculated using the CKD-EPI equation. For the IgAN cohort, follow-up information was reviewed through May 2024. The principal renal outcomes were:

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- Progression to chronic kidney disease stage 4.
- Development of end-stage renal disease.
- A reduction in eGFR of at least 75% from baseline.

CKD stage 4 was defined as an eGFR of 15–29 mL/min/1.73 m^2. ESRD required an eGFR below 15 mL/min/1.73 m^2 accompanied by a clinical plan for dialysis or kidney transplantation. The interval from biopsy to the occurrence of each renal endpoint was used to calculate event-free survival.

Statistical Analysis

Continuous variables were analyzed using independent-samples t-tests or Mann–Whitney U tests, depending on their distribution. Comparisons involving multiple groups were performed using ANOVA with Bonferroni correction or the Kruskal–Walli's test. Categorical variables were evaluated using chi-square or Fisher's exact tests. Receiver operating characteristic (ROC) analysis was used to determine the diagnostic performance and optimal KM55 threshold for identifying IgAN. Kaplan–Meier curves were generated to assess renal event-free survival. Univariate and multivariate Cox proportional hazards regression models were used to evaluate prognostic associations.

Statistical significance was established at pH less than .05.

Ethical Approval

The study was approved by the Institutional Review Board of Severance Hospital, Seoul, South Korea (IRB No. 4-2023-0868). Written informed consent was waived because of the retrospective study design.

RESULTS

Distribution of KM55 Expression Across Diagnostic Groups

Of the 114 renal biopsy specimens, 75 were diagnosed as IgAN and 39 as non-IgAN glomerular diseases. The IgAN group demonstrated substantially greater mesangial KM55 immunoreactivity than the non-IgAN group. Median staining scores were 3 (IQR, 2–3) and 1 (IQR, 0–1), respectively (p less than .001). Four non-IgAN specimens demonstrated a staining score of 2+; all belonged to patients with lupus nephritis.

ROC analysis demonstrated an area under the curve of 0.907 (95% CI, 0.855–0.959). A threshold of 2+ provided a sensitivity of 76.0% and specificity of 89.7%. Eighteen IgAN specimens exhibited only 1+ staining. These cases had lower circulating IgA concentrations than IgAN specimens with staining of at least 2+ (237.23 ± 78.91 versus 317.66 ± 136.87 mg/dL; p = .025). No significant differences were identified in initial immunofluorescence intensity or the interval between clinical presentation and biopsy (Figure 2).

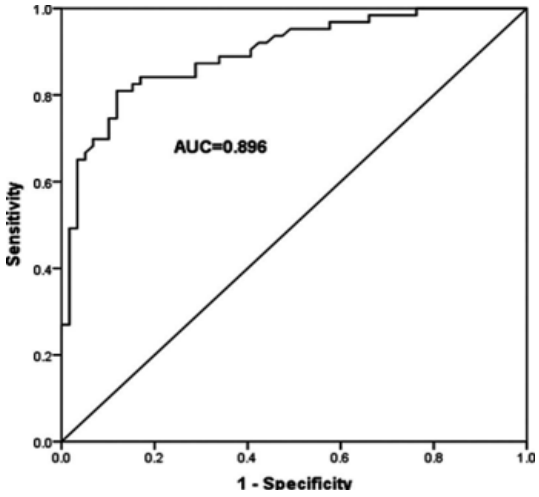


Figure 2: Diagnostic performance of KM55 staining in differentiating IgAN from non-IgAN disorders.

Association Between KM55 Staining and Histopathological Findings

Among the 75 IgAN specimens, 21 demonstrated M1, 30 E1, 48 S1, 11 T1/T2, and 29 C1/C2 findings. The distribution of Haas grades was two grade I, seven grade II, 42 grade III, 18 grade IV, and six grade V cases.

KM55 staining demonstrated significant associations with the M and T components of the Oxford classification. Specimens classified as M1 showed greater KM55 expression than M0 specimens (median, 3 versus 2; p = .017). Similarly, T1/T2 cases demonstrated higher staining scores than T0 cases (median, 3 versus 2; p = .049). No, statistically significant relationships were observed with E, S, or C scores. KM55 expression also did not differ significantly across Haas grades (p = .233).

Clinical Characteristics According to Individual KM55 Grades

The IgAN cohort was divided into four groups according to staining intensity: 1+ (n = 18), 2+ (n = 19), 3+ (n = 29), and 4+ (n = 9). Significant differences were identified in serum creatinine (p = .015), eGFR (p = .020), and serum albumin (p = .008). Higher KM55 grades generally accompanied increasing serum creatinine and declining eGFR. Serum albumin also showed a progressive reduction across the staining categories. UPCR and diastolic blood pressure increased numerically with greater staining intensity, although these differences did not reach statistical

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significance in the four-group comparison. Serum IgA concentrations differed across the groups (p = .050). The proportion of M1 cases also increased with stronger KM55 expression, reaching statistical significance (p = .042).

Comparison of KM55-High and KM55-low IgAN Groups

Based on the observed clinical and histological distribution, patients were classified into two categories:

- KM55-high: staining of 3+ or 4+ (n = 38).
- KM55-low: staining of 1+ or 2+ (n = 37).

The KM55-high group exhibited significantly greater UPCR, serum creatinine, and BUN, together with lower eGFR and serum albumin. Diastolic blood pressure was also higher in the KM55-high group. Serum IgA concentrations were elevated in this subgroup compared with the KM55-low group (334.55 ± 122.13 versus 260.41 ± 109.29 mg/dL; p = .012).

M1 lesions were more frequent in the KM55-high group (42.1% versus 13.5%; p = .012). The remaining Oxford parameters did not show statistically significant between-group differences.

Renal Outcomes and Survival Analysis

Renal deterioration occurred more frequently among patients with stronger KM55 staining. In the KM55-high group, 14 patients developed ESRD, 15 progressed to CKD stage 4, and 14 experienced a reduction in eGFR of at least 75%. The corresponding numbers in the KM55-low group were two, three, and two patients, respectively (Table 2).

Renal endpoint	Hazard ratio (95% CI)	p-value
ESRD	5.54 (1.26–24.45)	.024
CKD stage 4	4.71 (1.36–16.36)	.015
eGFR reduction ≥75%	6.15 (1.39–27.12)	.016

Table 2: Univariate Cox analysis demonstrated significantly increased risks associated with high KM55 expression.

Following adjustment for significant Oxford histological variables, KM55 staining was no longer independently associated with the three renal endpoints. Conversely, the T component retained independent prognostic significance for ESRD, CKD stage 4, and substantial eGFR reduction.

COVID-19-Associated IgAN

Nine patients were classified as having COVID-19-associated IgAN, while 66 belonged to the unrelated group. The COVID-19-associated group had higher serum albumin concentrations and a greater frequency of E1 lesions. No significant differences were identified in most other baseline clinical parameters. Median KM55 staining was lower in the COVID-19-associated group than in the unrelated group (1 versus 3; p = .022). No renal endpoint events were recorded in the COVID-19-associated subgroup during the available follow-up. The shorter observation period and limited number of cases restrict interpretation of this finding.

DISCUSSION

The present study demonstrates that mesangial KM55 immunoreactivity differs substantially between IgAN and other glomerular disorders exhibiting IgA positivity. Stronger staining was also associated with several indicators of impaired renal function and selected histological abnormalities. These findings support the potential use of KM55 immunohistochemistry as an additional diagnostic method in renal biopsy assessment.

The biological relevance of Gd-IgA1 is supported by the established relationship between abnormal IgA1 glycosylation, antiglycan antibody formation, and mesangial immune-complex deposition. These processes contribute to glomerular inflammation and progressive tissue injury. Consequently, identifying Gd-IgA1 directly within renal tissue may provide useful information about the immunopathological features of IgAN [10]. Previous investigations have demonstrated that KM55 can recognize Gd-IgA1 without depending on lectin-based detection methods. Its application in renal biopsy specimens has revealed mesangial staining in primary and secondary IgA-associated diseases, although staining intensity and diagnostic specificity vary between pathological entities [11]. These observations are consistent with the present findings, in which the IgAN group demonstrated substantially stronger KM55 expression than the non-IgAN group.

The diagnostic ROC analysis produced an AUC of 0.907, indicating good discriminatory performance within the investigated cohort. A staining threshold of 2+ provided 76.0% sensitivity and 89.7% specificity. Nevertheless, 18 IgAN specimens showed only faint 1+ staining. This finding indicates that a negative or weak result cannot independently exclude IgAN. Differences in tissue sampling, distribution of mesangial deposits, and staining interpretation may contribute to such variability. Four lupus nephritis specimens demonstrated 2+ KM55 immunoreactivity despite being classified as non-IgAN.

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Previous investigations have also identified Gd-IgA1 expression in selected non-IgAN conditions, indicating that KM55 positivity is not entirely disease-specific [12]. Similarly, diagnostic overlap between lupus nephritis and IgAN has been documented in studies examining Gd-IgA1 immunostaining [13]. Therefore, interpretation should incorporate the distribution of immunoreactivity, immunofluorescence findings, ultrastructural characteristics, and clinical information.

Electron microscopy remains valuable when distinguishing genuine mesangial deposits from staining involving adjacent glomerular compartments. In the present series, some lupus nephritis specimens demonstrated deposits in subepithelial or intramembranous locations without convincing mesangial deposits. This observation raises the possibility that non-specific or anatomically overlapping staining may influence the apparent KM55 score. The association between KM55 expression and the Oxford M component provides further insight into the relationship between abnormal IgA1 deposition and mesangial injury. Greater staining was observed in specimens exhibiting mesangial hypercellularity. This finding is compatible with the proposed biological effects of Gd-IgA1-containing immune complexes, which can stimulate mesangial cellular responses and extracellular matrix production.

The relationship with the T component was also statistically significant. Increased tubular atrophy and interstitial fibrosis represent chronic structural damage and are recognized indicators of progressive renal disease. The observed association may reflect the relationship between mesangial immune-complex deposition and accumulated renal injury. However, the retrospective design does not establish whether stronger KM55 expression directly contributes to chronic tissue damage or accompanies more advanced disease. The clinical comparisons further demonstrated that patients with stronger KM55 expression had higher serum creatinine and BUN, greater proteinuria, lower eGFR, and reduced serum albumin. Increased diastolic blood pressure and circulating IgA concentrations were also observed in the KM55-high subgroup. These findings suggest that stronger tissue immunoreactivity occurs more frequently in patients with an unfavorable clinical profile.

Previous investigations examining serum Gd-IgA1 have reported associations with clinical disease activity and long-term renal outcomes. However, circulating concentrations do not necessarily correspond directly to the quantity of deposited Gd-IgA1 within the kidney [14]. Tissue-based grading may therefore provide complementary information, although its relationship with serum measurements requires additional investigation. The prognostic analysis demonstrated significantly increased risks of ESRD, CKD stage 4, and substantial eGFR reduction among patients with KM55 scores of at least 3+. The separation between the high- and low-staining groups was more apparent than that observed across individual staining categories. These observations suggest that the proposed threshold may be useful for exploratory clinical risk assessment.

However, KM55 staining did not remain independently significant in the adjusted Cox regression models. In contrast, the T component retained an independent association with all three renal endpoints. This distinction is clinically important because the unadjusted relationship between KM55 expression and renal deterioration may partly reflect its association with established histological damage. The Oxford classification was developed to provide reproducible histological assessment and improve prognostic evaluation in IgAN [15]. Subsequent validation and classification updates have reinforced the importance of standardized reporting of renal lesions [16]. The present results suggest that KM55 staining may complement established pathological assessment, but the available evidence does not support its incorporation as an independent prognostic component.

The findings should also be interpreted alongside previous studies evaluating KM55 immunofluorescence. Investigations have reported Gd-IgA1 expression in several IgA-associated renal diseases, including IgA vasculitis and selected secondary conditions [17]. Other studies have questioned the specificity of Gd-IgA1 staining for primary IgAN, emphasizing the importance of integrating immunohistochemical findings with conventional pathological evaluation [18]. The COVID-19-associated subgroup demonstrated lower median KM55 staining than the unrelated IgAN group. This difference may reflect variations in clinical presentation, timing of biopsy, or underlying immunological mechanisms. However, only nine patients belonged to the COVID-19-associated group, and their shorter follow-up limits assessment of long-term outcomes. Reports of IgAN following COVID-19 vaccination or infection have described variable clinical and pathological presentations [19]. A retrospective cohort investigation has also examined the renal safety of COVID-19 vaccination among individuals with established IgAN [20]. In addition, published case reports have documented biopsy-confirmed IgAN following mRNA vaccination, including mesangial

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immune deposits [21]. Reviews of reported post-infection and post-vaccination cases have described heterogeneous clinical courses, making it difficult to establish a consistent relationship between COVID-19 exposure and subsequent renal prognosis [22].

Clinical Relevance

KM55 immunohistochemistry may be useful when evaluating renal biopsies with mesangial IgA positivity, particularly when the distinction between IgAN and other IgA-containing glomerular disorders is uncertain. The observed threshold of 2+ provides a potential diagnostic reference within the investigated population. Nevertheless, the presence of weak staining in confirmed IgAN cases and moderate staining in selected lupus nephritis specimens demonstrates that the result should not be interpreted independently. A high KM55 score may also identify patients with greater clinical and histological disease burden. Its use alongside serum creatinine, eGFR, proteinuria, and Oxford classification findings could contribute to a more comprehensive description of biopsy characteristics. Established diagnostic and risk-assessment recommendations continue to rely on integrated clinical and pathological evaluation rather than a single tissue biomarker [23].

Study Limitations

Several limitations should be acknowledged.

First, the retrospective design and relatively small sample size may have influenced the statistical power of the comparisons. Second, the study was conducted at a single institution, limiting the generalizability of the diagnostic threshold to other populations and laboratories.

Third, KM55 staining was evaluated using a semiquantitative grading system. Differences in interpretation between observers may have affected score allocation. Digital image analysis and automated quantification could improve consistency in future investigations.

Fourth, serum IgA and complement measurements were unavailable for some participants, restricting the completeness of certain subgroup comparisons.

Finally, the KM55-high subgroup demonstrated significant associations with renal outcomes in univariate analyses, but these associations were not independently significant after adjustment for histological variables. The prognostic contribution of KM55 therefore remains uncertain.

Prospective multicenter investigations with standardized staining protocols, reproducibility testing, and longer follow-up are required to establish its diagnostic and prognostic applications.

CONCLUSION

Mesangial KM55 immunoreactivity provides useful information about Gd-IgA1 deposition in renal biopsy specimens and may assist in distinguishing IgA nephropathy from other glomerular disorders with mesangial IgA positivity. Stronger staining was associated with impaired renal function, increased proteinuria, lower serum albumin, and greater mesangial hypercellularity. Patients with KM55 scores of 3+ or 4+ also experienced more frequent progression to advanced chronic kidney disease and end-stage renal disease in univariate survival analyses. Nevertheless, KM55 expression did not retain independent prognostic significance after adjustment for established histological variables, whereas tubular atrophy and interstitial fibrosis remained independently associated with renal deterioration. These findings indicate that KM55 immunohistochemistry may complement conventional pathological assessment rather than replace established diagnostic and prognostic parameters. Standardized staining protocols, reproducibility assessment, and prospective multicenter studies are necessary before its routine incorporation into renal biopsy reporting can be recommended.

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