Correlation Between Partial Blood Indices and 24-Hour Urinary Protein Quantification in 3,774 Children with IgA Vasculitis Nephritis: Post-print

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Abstract

Background IgA vasculitis nephritis (IgAVN) is one of the common systemic small-vessel vasculitides in childhood; however, comprehensive clinical studies on the relationship between blood indicators and urinary protein quantification in affected children are limited.

Objective To investigate the changing patterns of 24-hour urinary protein quantification and its correlation with selected blood indicators in children with IgAVN.

Methods Children with IgAVN who visited the First Affiliated Hospital of Henan University of Chinese Medicine between 2013 and 2023 were selected, and their 24-hour urinary protein quantification, basic information, and relevant laboratory examination indicators were collected for retrospective analysis. Mann-Whitney test, Kruskal-Wallis test, and Spearman rank correlation analysis were employed to explore the relationship between 24-hour urinary protein quantification and blood indicators in these children.

Results After data curation, a total of 3,774 children with IgAVN were included, comprising 2,230 males with an onset age of 10.0 (7.0, 12.0) years and 1,544 females with an onset age of 10.0 (7.0, 12.0) years. No statistically significant differences were observed in 24-hour urinary protein quantification among HSPN children of different genders, among different ranges of monocyte percentage (M%) and mean corpuscular hemoglobin concentration (MCHC) in complete blood count, different ranges of alanine aminotransferase (ALT) in liver and kidney function tests, different ranges of C3, C4, immunoglobulin A (IgA), and immunoglobulin M (IgM) in the six immunological items, or different ranges of CD3%, CD3CD8%, and CD4/CD8 in T-cell subsets ($P>0.05$). Spearman rank

correlation analysis revealed that 24-hour urinary protein quantification was negatively correlated with age (rs=-0.179, P<0.001). 24-hour urinary protein quantification was positively correlated with white blood cell count (WBC), platelet count (PLT), neutrophil percentage (N%), and erythrocyte sedimentation rate (ESR) in complete blood count; with aspartate aminotransferase (AST), blood urea nitrogen (BUN), lactate dehydrogenase (LDH), triglycerides (TG), and cholesterol (CHOL) in liver and kidney function indicators; with immunoglobulin E (IgE) in the six immunological items; with D-dimer (D2) and thrombin time (TT) in coagulation indicators; and with CD3, CD3CD4, and CD3CD8 in T-cell subsets (P<0.05). It was negatively correlated with red blood cell count (RBC), hemoglobin (Hb), lymphocyte percentage (L%), and eosinophil percentage (E%) in complete blood count; with C-reactive protein (CRP); with total protein (TP), albumin (ALB), direct bilirubin (DBIL), alkaline phosphatase (ALP), creatinine (Cr), uric acid (UA), and calcium (Ca) in liver and kidney function; with IgG in the six immunological items; with international normalized ratio (INR), activated partial thromboplastin time (APTT), prothrombin time (PT), and fibrinogen (FIB) in coagulation indicators; and with CD3CD4% in T-cell subsets (P<0.05).

Conclusion This study found that 24-hour urinary protein quantification in children with IgAVN is significantly associated with multi-system indicators: it is positively correlated with renal function impairment (BUN, LDH), lipid metabolism disorders (TG, CHOL), Th1 immune polarization (CD3CD8+), and hypercoagulable state (D2, TT); and negatively correlated with hepatic synthetic function (ALB, TP), immune regulation (CD3CD4%), and coagulation factors (FIB). These findings provide a clinical basis for further elucidating the pathological mechanisms of IgAVN, constructing a clinical monitoring and early warning system, and optimizing treatment strategies.

Full Text

Correlation of Selected Blood Biomarkers with 24-Hour Urine Protein Excretion in 3,774 Pediatric Patients with IgA Vasculitis Nephritis

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Abstract

Background: IgA vasculitis nephritis (IgAVN) represents one of the most common systemic small-vessel vasculitides in childhood, yet comprehensive investigations into the relationship between hematological parameters and urinary protein quantification remain limited.

Objective: To investigate the patterns of 24-hour urinary protein excretion and their correlation with selected blood biomarkers in pediatric IgAVN patients.

Methods: We conducted a retrospective analysis of IgAVN patients treated at the First Affiliated Hospital of Henan University of Chinese Medicine between 2013 and 2023. Clinical data including 24-hour urine protein quantification, demographic information, and relevant laboratory parameters were collected. Mann-Whitney U test, Kruskal-Wallis test, and Spearman rank correlation analysis were employed to examine associations between 24-hour urine protein excretion and hematological indicators.

Results: Following data curation, 3,774 IgAVN pediatric patients were included (2,230 males and 1,544 females), with a median age of onset of 10.0 (7.0, 12.0) years for both genders. No statistically significant differences in 24-hour urine protein excretion were observed across gender, monocyte percentage (M%) and mean corpuscular hemoglobin concentration (MCHC) ranges in complete blood count, alanine aminotransferase (ALT) ranges in liver function tests, C3, C4, immunoglobulin A (IgA), and immunoglobulin M (IgM) ranges in immunological panels, or CD3%, CD3CD8%, and CD4/CD8 ranges in T-cell subsets ($P>0.05$). Spearman rank correlation analysis revealed a negative correlation between 24-hour urine protein excretion and age ($r =-0.179$, $P<0.001$). Positive correlations were identified with white blood cell count (WBC), platelet count (PLT), neutrophil percentage (N%), erythrocyte sedimentation rate (ESR), aspartate aminotransferase (AST), blood urea nitrogen (BUN), lactate dehydrogenase (LDH), triglycerides (TG), cholesterol (CHOL), immunoglobulin E (IgE), D-dimer (D2), thrombin time (TT), and T-cell subsets CD3, CD3CD4, CD3CD8 ($P<0.05$). Negative correlations were found with red blood cell count (RBC), hemoglobin (Hb), lymphocyte percentage (L%), eosinophil percentage (E%), C-reactive protein (CRP), total protein (TP), albumin (ALB), direct bilirubin (DBIL), alkaline phosphatase (ALP), creatinine (Cr), uric acid (UA), calcium (Ca), immunoglobulin G (IgG), international normalized ratio (INR), activated partial thromboplastin time (APTT), prothrombin time (PT), fibrinogen (FIB), and CD3CD4% ($P<0.05$).

Conclusion: This study demonstrates significant associations between 24-hour urine protein excretion and multi-systemic parameters in IgAVN patients: positive correlations with renal impairment markers (BUN, LDH), lipid metabolism disorders (TG, CHOL), Th1 immune polarization (CD3CD8), and hypercoagulable state (D2, TT); and negative correlations with hepatic synthetic function

(ALB, TP), immune regulation (CD3CD4%), and coagulation factors (FIB). These findings provide clinical evidence for elucidating IgAVN pathological mechanisms, constructing clinical monitoring and early warning systems, and optimizing therapeutic strategies.

Keywords: IgA vasculitis nephritis; child; 24-hour urine protein quantification; complete blood count; liver and kidney function; six coagulation indices; six immunological indices; T-cell subsets

Introduction

IgA vasculitis (IgAV), previously known as Henoch-Schönlein purpura, is a common systemic small-vessel vasculitis in childhood, typically manifesting as palpable purpura on the lower extremities, arthralgia, abdominal pain, and gastrointestinal symptoms, with a generally self-limiting course[1]. IgA vasculitis nephritis (IgAVN) represents a severe complication of IgAV, clinically presenting as hematuria, proteinuria, and renal function impairment, affecting 20-60% of children with IgAV[2]. Adult IgAVN demonstrates even higher incidence (45-85%) and poorer prognosis, with end-stage renal disease (ESRD) risk reaching 32%[3]. The core pathological mechanisms of both IgAV and IgAVN involve deposition of galactose-deficient IgA1 (Gd-IgA1) immune complexes in small vessels throughout the skin, joints, gastrointestinal tract, and kidneys[1]. IgAVN specifically denotes renal involvement characterized by IgA complex deposition in glomeruli and immune-mediated inflammatory responses[3].

Recent studies indicate increasing incidence of pediatric IgAVN, with 1-7% of patients experiencing disease recurrence despite clinical remission of proteinuria and hematuria following treatment[4]. Without timely detection and standardized management, 10-20% of affected children ultimately develop renal impairment during adolescence or adulthood[5], posing significant threats to pediatric health and establishing this population as high-risk for future chronic kidney disease (CKD)[6–7]. Clinical assessment of renal damage primarily relies on urinalysis, renal function tests, and renal biopsy; however, renal biopsy carries considerable risks with limited acceptance, while routine urinalysis exhibits lag time and faces challenges with patient compliance. Numerous investigators have dedicated efforts to identifying high-risk factors for IgAVN-related renal damage and preventive strategies, encompassing epidemiological characteristics, ancillary clinical examinations, and predictive risk factor analyses[8–11]. However, available laboratory data remain relatively limited, and although traceable to parameters influencing 24-hour urine protein severity, these have not been systematically categorized or thoroughly investigated. Therefore, this study aimed to screen and comprehensively analyze laboratory parameters influencing disease patterns in IgAVN patients, providing healthcare providers and families with evidence for timely protective measures, early diagnosis, and prompt treatment.

Methods

Data Sources We selected IgAVN patients treated at the First Affiliated Hospital of Henan University of Chinese Medicine between 2013 and 2023. After applying inclusion and exclusion criteria, 3,774 eligible IgAVN patients were identified from initial hospitalization records. This study was approved by the Ethics Committee of the First Affiliated Hospital of Henan University of Chinese Medicine (Approval No.: 2023HL-281-01).

Inclusion criteria: (1) Met diagnostic criteria for IgAVN according to integrated Chinese and Western medicine guidelines, with $ $3 episodes of proteinuria within one week; (2) Age 1-18 years; (3) Pre-treatment 24-hour urine protein quantification results available, with values $ $150 mg/d; (4) Medical record completeness $ $90%, including demographic data (age, gender), laboratory parameters (24-hour urine protein quantification, complete blood count, liver/kidney function, six coagulation indices, six immunological indices, T-cell subsets), and complete treatment regimens (glucocorticoids, Tripterygium glycosides, immunosuppressants).

Exclusion criteria: (1) Comorbid autoimmune diseases with intrinsic renal involvement or urinary abnormalities, such as immune thrombocytopenia, systemic lupus erythematosus, psoriasis, IgA nephropathy, or nephrotic syndrome; (2) Primary cardiac, hepatic, renal, or hematopoietic system diseases, and psychiatric or neurological disorders; (3) Acute or chronic immunodeficiency diseases.

Diagnostic criteria followed the "Guidelines for Integrated Chinese and Western Medicine Diagnosis and Treatment of Pediatric Henoch-Schönlein Purpura Nephritis (2023)"[4]. Clinical classification included isolated hematuria or proteinuria, hematuria with proteinuria, rapidly progressive glomerulonephritis, acute nephritic syndrome, nephrotic syndrome, and chronic nephritis. Traditional Chinese medicine syndrome differentiation comprised five primary patterns (damp-heat invasion, yin deficiency with effulgent fire, lung-spleen qi deficiency, spleen-kidney yang deficiency, yin deficiency with effulgent fire) and three concurrent patterns (blood stasis, wind-heat, blood heat). Renal pathological diagnosis followed the International Study of Kidney Disease in Children (ISKDC) grading system (Grades I-VI) based on glomerular lesion severity and crescent formation proportion[5].

Data Collection and Storage Clinical data were retrieved from the Pediatric IgAVN Registry Database of Henan University of Chinese Medicine, including demographic information (gender, age at onset, height, weight) and laboratory parameters. Valid data (structural and non-structural) were deduplicated, organized, and stored using Microsoft Excel.

Laboratory parameters included: - **Complete blood count:** WBC, monocyte percentage (M%), RBC, neutrophil percentage (N%), lymphocyte percentage (L%), eosinophil percentage (E%), MCHC, Hb, PLT, CRP, ESR - **Liver**

and kidney function: TP, ALB, ALT, AST, Cr, ALP, BUN, UA, LDH, DBIL, TG, CHOL, Ca - **Immunological panel:** C3, C4, IgA, IgE, IgG, IgM - **Coagulation panel:** D-dimer (D2), INR, APTT, TT, PT, FIB - **T-cell subsets:** CD3, CD3CD4, CD3CD4%, CD3CD8, CD3CD8%, CD4/CD8

Statistical Analysis Data analysis was performed using IBM SPSS Statistics 26.0 and GraphPad Prism 8.0. Continuous variables underwent normality testing; normally distributed data were expressed as mean ± standard deviation ($\bar{x}\pm s$) and compared using independent t-tests, while non-normally distributed data were presented as median (P25, P75) and compared using Mann-Whitney U test (two groups) or Kruskal-Wallis test (three or more groups). Categorical variables were expressed as frequencies and compared using ^{2} test or Fisher's exact test. Correlation analysis employed Spearman rank correlation. Statistical significance was defined as $P<0.05$.

Results

Relationship Between 24-Hour Urine Protein Excretion and Demographics Following data curation, 3,774 IgAVN patients were included: 2,230 males (median age 10.0 [7.0, 12.0] years; height 141.8$\pm$20.7cm; $weight$32.0[25.0, 43.0]kg)and1, 544$females$($med
cm; weight 30.5 [24.0, 42.0] kg). Age distribution: 590 patients aged (1,6] years, 2,287 aged (6,12] years, and 897 aged (12,18] years.

No significant gender difference in 24-hour urine protein excretion was observed ($P>0.05$). However, significant age-related differences were detected ($P<0.001$) . Spearman analysis revealed a negative correlation between 24-hour urine protein excretion and age ($r =-0.179$, $P<0.001$).

Distribution of 24-Hour Urine Protein Excretion Across Complete Blood Count Ranges Significant differences in 24-hour urine protein excretion were observed across WBC, RBC, Hb, PLT, N%, L%, E%, CRP, and ESR ranges ($P<0.05$), but not across M% or MCHC ranges ($P>0.05$) .

Distribution Across Liver and Kidney Function Parameter Ranges Significant differences were found across ALB, AST, ALP, BUN, Cr, UA, LDH, DBIL, TG, CHOL, TP, and Ca ranges ($P<0.05$), but not across ALT ranges ($P>0.05$) .

Distribution Across Immunological Parameter Ranges Significant differences were observed across IgE and IgG ranges ($P<0.005$), but not across C3, C4, IgA, or IgM ranges ($P>0.005$) .

Distribution Across Coagulation Parameter Ranges Significant differences were identified across D2, INR, APTT, TT, PT, and FIB ranges ($P<0.001$) .

Distribution Across T-Cell Subset Ranges Significant differences were found across CD3, CD3CD4, CD3CD4%, and CD3CD8 ranges ($P<0.05$), but not across CD3%, CD3CD8%, or CD4/CD8 ranges ($P>0.05$) .

Correlation Analysis Between 24-Hour Urine Protein Excretion and Laboratory Parameters Spearman rank correlation analysis revealed: - **Positive correlations** ($P<0.05$) with WBC, PLT, N%, ESR, AST, BUN, LDH, TG, CHOL, IgE, D2, TT, CD3, CD3CD4, CD3CD8, and CD3CD8% - **Negative correlations** ($P<0.05$) with RBC, Hb, L%, E%, CRP, TP, ALB, DBIL, ALP, Cr, UA, Ca, IgG, INR, APTT, PT, FIB, and CD3CD4%

Discussion

IgAV is a common IgA-mediated systemic vasculitis in childhood, primarily affecting the skin, joints, gastrointestinal tract, and kidneys[12]. IgAVN, a specific manifestation of IgAV, represents glomerular damage mediated by immune-mediated vasculitis, characterized by increased galactose-deficient IgA1 and deposition of circulating immune complexes in the mesangial region. The pathogenesis involves complex interactions among genetic susceptibility, immune dysregulation, complement activation, and cell-mediated inflammatory responses[13]. Human leukocyte antigen (HLA) polymorphisms demonstrate significant associations with IgAVN susceptibility; HELD et al.[14] identified HLA-DRB111 and HLA-DRB113 alleles as significantly associated with IgAVN, particularly the haplotype HLA-DRB101:01$_{\text{DQB105:01}}$DQA101:01. Additionally, HLA-B35 may increase IgAVN risk[15]. Beyond genetic factors, aberrant glycosylation of Gd-IgA1 leads to production of anti-Gd-IgA1 IgG autoantibodies, forming immune complexes that deposit in glomerular mesangium—the core "four-hit hypothesis" encompassing Gd-IgA1 synthesis, autoantibody response, immune complex formation, and post-deposition complement activation[16]. These complexes activate the alternative complement pathway, consuming C3 and C4 and triggering inflammatory cascades[17]. Post-complement activation, macrophages polarize toward pro-inflammatory M1 phenotype, secreting TNF-α and IL-6 that exacerbate glomerular injury while enhancing cell-mediated immunity through monocyte regulation[17]. Cytotoxic T lymphocyte-mediated cellular toxicity further contributes to renal damage, as infiltrating CTLs and natural killer cells induce glomerular apoptosis via perforin and granzyme B release[17]. Respiratory or gastrointestinal infections serve as important triggers, activating Toll-like receptor 4 (TLR4) to initiate innate immune responses that release NF- B and MAPK inflammatory mediators, with TLR4 overexpression directly correlating with glomerular damage[12].

This real-world clinical data analysis of 3,774 IgAVN patients first examined categorical ranges of complete blood count, liver/kidney function, coagulation, immunological, and T-cell subset parameters, then investigated correlations between individual parameters and 24-hour urine protein excretion to inform early diagnosis and treatment.

Age-related findings: The negative correlation between 24-hour urine protein excretion and age ($r = -0.179$, $P<0.001$) suggests younger patients face higher renal injury risk, potentially related to developmental stage-specific immune characteristics and immature immune systems. Traditional Chinese medicine theory posits that pediatric constitution commonly features "lung-spleen-kidney deficiency," facilitating disease onset and rapid progression. Immunological studies demonstrate reduced IgA, IgG, and $CD4^+$ T cells with elevated $CD8^+$ T cells in preschool children (ages 2-6), resulting in weaker immune responses and infection susceptibility[18]. Our finding of significantly higher 24-hour urine protein excretion in children under 6 years corroborates this, indicating that younger IgAVN patients have impaired capacity to counteract inflammatory damage from Gd-IgA1 complex deposition.

Hematological parameters: Positive correlations with WBC, neutrophils, PLT, and ESR ($r>0$, $P<0.05$) reflect immune-inflammatory processes. Neutrophils, key components of innate immunity, respond rapidly to pathogens and participate in inflammatory reactions. In IgAVN, IgA1 immune complexes bind CD89, activating neutrophils to release myeloperoxidase and elastase that damage vascular endothelium; excessive neutrophil aggregation perpetuates inflammation and exacerbates renal tissue injury[19]. Monocyte-macrophages release TNF-α, IL-6, and IL-8 to activate inflammatory responses, while T-cell subsets promote eosinophil recruitment and activation. Activated eosinophils secrete leukotriene C4, prostaglandin D2, and chemokines that participate in IgAVN inflammation[20–22]. ESR elevation and PLT aggregation/adhesion due to vasculitic injury further contribute to glomerular basement membrane damage—the primary cause of hematuria and proteinuria in IgAVN.

Liver and kidney function: Positive correlations with AST, BUN, LDH, TG, and CHOL ($r>0$, $P<0.05$) and negative correlations with TP, ALB, DBIL, ALP, Cr, UA, and Ca ($r<0$, $P<0.05$) indicate that urine protein levels rise with AST and BUN elevation while decreasing with TP and ALB increase. AST and LDH, primarily located in cardiomyocytes but also present in liver, skeletal muscle, and kidney, signal tissue damage and metabolic abnormalities when elevated. Elevated TG and CHOL correlate with $CD146^+$ T cell-mediated inflammatory injury, contributing to glomerular basement membrane damage[23]. Studies show that refractory nephrotic syndrome patients exhibit reduced AST, TG, and CHOL following treatment-induced proteinuria reduction, supporting our findings and suggesting these markers may indirectly reflect renal function[24]. BUN elevation indicates glomerular filtration impairment, with higher levels correlating with more severe proteinuria and hematuria. ALP elevation primarily reflects rapid growth in younger children[25], while reduced Ca decreases vascular permeability, weakening glomerular barrier function and facilitating protein leakage.

Immunological parameters: Positive correlation with IgE and negative correlation with IgG ($P<0.05$) reflect immunoglobulin dynamics. IgE, normally comprising only 0.02% of serum antibodies, increases dramatically in allergic

diseases. In IgAVN, exogenous allergens trigger B lymphocyte differentiation into plasma cells that synthesize IgE, which binds high-affinity receptors on mast cells and basophils. Subsequent allergen exposure induces degranulation, releasing histamine and leukotrienes that cause systemic vasculitis, skin purpura, arthralgia, abdominal pain, and renal damage[26]. Th2 cell predominance in IgAVN stimulates B cell proliferation and IgE synthesis, driving inflammatory responses[27]. Conversely, high 24-hour urine protein excretion correlates with low IgG, likely due to immune complex consumption[28].

T-cell immunity: Positive correlations with CD3, CD3CD8, and CD3CD8% ($P<0.05$) and negative correlations with CD3CD4% and CD4/CD8 ($P<0.05$) reflect T-cell dynamics. CD3, a transmembrane protein forming the TCR-CD3 complex on all mature T cells, serves as a T lymphocyte marker[28]. In autoimmune diseases, self-antigen recognition activates and proliferates T lymphocytes, elevating CD3 expression. Viral infections similarly increase CD3 expression, and as important IgAVN triggers, activate $CD4^+$ T cells to secrete cytokines that assist B cell antibody production while activating $CD8^+$ lymphocytes to kill virus-infected cells[29]. Thus, elevated CD3, CD3CD8, and CD3CD8% indicate immune hyperactivity or viral infection, representing acute IgAVN with high urine protein and severe disease. Conversely, elevated CD3CD4% and CD4/CD8 suggest immune activation favoring B cell antibody production, characteristic of early-stage autoimmune disease with lower proteinuria.

Coagulation parameters: Negative correlations with INR, APTT, PT, and FIB ($P<0.001$) and positive correlation with TT ($P<0.05$) reflect hemodynamic alterations. Elevated vascular pressure and blood viscosity reduce glomerular blood flow, initiating renal pathology. Studies show primary nephrotic syndrome proteinuria correlates positively with APTT, FIB, PT, and INR in hypercoagulable states[29], though therapeutic interventions may reverse these relationships[30–32]. Abnormal erythrocyte metabolism causes microcirculatory disturbances, while platelet activation and thrombosis alter hemodynamics[33–34]. From a traditional Chinese medicine perspective, blood stasis represents a key pathological mechanism throughout IgAVN progression and a major factor in disease recurrence.

Integrated model: Our correlation model ($P<0.05$) reveals that inflammatory activation markers (WBC, N%, ESR), renal injury markers (BUN, LDH), lipid metabolism disorder indices (TG, CHOL), and hypercoagulability markers (D2, TT) positively correlate with proteinuria, while nutritional-metabolic (ALB, TP, Hb) and immune regulatory markers (CD3CD4%) correlate negatively. This suggests IgAVN involves a vicious cycle of "immune dysregulation triggering metabolic reprogramming, metabolic abnormalities activating coagulation cascades, and coagulation disturbances exacerbating immune damage." Inflammatory markers may trigger metabolic changes and coagulation pathway activation; metabolic disorders may further impair immune function, intensify inflammation, and promote coagulation abnormalities; elevated coagulation markers may cause microthrombi formation, worsening renal injury and releas-

ing more inflammatory factors. This provides new evidence for the "immune-metabolism-coagulation" interplay in IgAVN pathogenesis.

Clinical implications: We propose incorporating cross-indicator panels such as CD3CD8/IgE-D2 combinations and AST/ALB gradients into monitoring systems. The immune imbalance characterized by $CD3CD8^+$ positively correlating (r =0.132) and $CD3CD4^+$ negatively correlating (r =-0.109) with proteinuria suggests Th1/Th2 shift as a potential therapeutic target. Based on strong associations between 24-hour protein excretion and the coagulation-metabolism axis (INR, APTT, PT, FIB, TG, CHOL) and liver-kidney axis (AST, Cr, UA), we recommend augmenting conventional immunosuppression with anticoagulation (e.g., low molecular weight heparin) and lipid modulation (e.g., statins). The negative correlation with calcium provides laboratory support for vitamin D analogs' renoprotective application.

In summary, this real-world study of 3,774 IgAVN patients elucidates multi-dimensional associations between 24-hour urine protein excretion and blood biomarkers, providing laboratory evidence for understanding pathological mechanisms, establishing monitoring systems, and optimizing treatment. Limitations include the single-center retrospective design and lack of treatment response and prognosis data. Future directions should incorporate dynamic monitoring, mechanistic studies, and multi-center validation to provide comprehensive evidence for precision medicine in IgAVN.

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