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ORIGINAL RESEARCH

Time-Weighted Average Proteinuria and Renal Function Decline in IgA Nephropathy: A Retrospective Cohort Study

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Background: IgA nephropathy (IgAN) is the leading primary glomerulonephritis globally, with many patients advancing to end-stage renal disease. Proteinuria is a key predictor of renal function decline in IgAN, yet the best method for long-term assessment is unclear. This study explores the relationship between time-weighted average proteinuria (TWAP), a novel metric of cumulative proteinuria exposure, and renal function decline in IgAN patients.

Methods: This single-center retrospective cohort study encompassed 549 patients with biopsy-confirmed primary IgAN from Shenzhen Second People's Hospital from 2011 to 2023. TWAP served as the primary exposure variable, calculated using the protein-creatinine ratio values, while changes in estimated glomerular filtration rate (eGFR) constituted the primary outcome. Covariates included age, sex, blood pressure, and mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), tubular atrophy/interstitial fibrosis (T), and crescents (C) (known as the Oxford Classification MEST-C score system). The associations between TWAP and eGFR trajectories were analyzed using Generalized Additive Mixed Models.

Results: In patients with baseline eGFR 15–60 mL/min/1.73m², higher TWAP levels correlated with accelerated eGFR decline. Compared to TWAP < 0.3 g/g, TWAP 0.3–0.5 g/g, 0.5–1 g/g, and ≥1 g/g were associated with additional annual eGFR declines of 2.04 (95% CI: −3.72 to −0.35), 3.38 (95% CI: −5.12 to −1.65), and 4.04 (95% CI: −6.61 to −1.47) mL/min/1.73m²/year, respectively. For eGFR ≥60 mL/min/1.73m², only TWAP ≥1 g/g significantly accelerated eGFR decline 5.70 (95% CI: −6.84 to −4.55) mL/min/1.73m²/year.

Conclusion: TWAP significantly predicts renal function decline in IgAN, especially in patients with pre-existing renal dysfunction. Maintaining TWAP below 0.3 g/g may significantly slow disease progression, emphasizing the importance of stringent proteinuria control in IgAN management.

Keywords: IgA nephropathy, mixed methods, renal function, time-weighted average proteinuria, (TWAP)

Introduction

IgA nephropathy (IgAN) is the most prevalent primary glomerulonephritis worldwide, with higher rates in East and Pacific Asia compared to North America and Europe.[1–3] In China, IgAN accounts for 45.26% of primary glomerulonephritis, with approximately 20–30% of patients progressing to end-stage renal disease (ESRD) within two decades of diagnosis.[4,5]

Proteinuria has emerged as a critical predictor of renal function decline in IgAN.[6–9] Traditional assessment methods using single-point measurements or simple averages fail to capture the dynamic nature of proteinuria and its cumulative impact on kidney function. This limitation necessitates more comprehensive approaches to evaluating long-term proteinuria exposure. Time-weighted average proteinuria (TWAP) represents an innovative method to assess cumulative proteinuria burden. Analogous to time-weighted average albuminuria in diabetes research,[10] TWAP aims to more

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accurately reflect proteinuria's longitudinal impact on renal outcomes. Given the heterogeneous progression of IgAN and proteinuria's pivotal role in disease management, exploring TWAP could provide valuable insights for clinical practice.

To address this gap, we conducted a single-center retrospective cohort study evaluating the association between TWAP and renal function changes in IgAN patients. By analyzing the correlation between TWAP and estimated glomerular filtration rate (eGFR) changes, we aim to elucidate the impact of long-term proteinuria exposure and identify potential therapeutic targets.

Materials and Methods

Study Design and Patients

This was a single-center retrospective cohort study included patients with biopsy-proven primary IgAN as recorded in the IgAN Database of Shenzhen Second People's Hospital between January 1, 2011, and December 31, 2023. Patients with a secondary cause of IgAN, such as Henoch–Schönlein purpura, systemic lupus erythematosus, or chronic liver disease, were excluded, as were those without follow-up data for urine protein-creatinine ratio or eGFR, a baseline eGFR < 15 mL/min/1.73 m^2, or a follow-up time < 6 months. Baseline demographic, clinical, and laboratory data were collected at the time of renal biopsy. Follow-up data were obtained from regular outpatient visits or hospitalizations.

This study was approved by the Medical Ethics Committee of Shenzhen Second People's Hospital (No. 20211108001-FS01) and conducted ethically in accordance with the World Medical Association Declaration of Helsinki. All subjects provided their written informed consent before enrollment.

Variables

The primary exposure variable was time-weighted average proteinuria (TWAP), calculated using the protein-creatinine ratio from morning urine samples analyzed by an automated biochemical analyzer. Protein-creatinine ratio values were recorded at each follow-up visit. TWAP was then computed using the following formula:

$$\mathrm{TWAP} = \Sigma(\mathrm{PCRi} \times \mathrm{Ti}) / \Sigma\mathrm{Ti}$$

Where PCRi is the protein-creatinine ratio value at visit i, and Ti is the time interval between visit i and the next visit (or end of follow-up for the last visit).

Patients were categorized into four groups based on their TWAP values for analysis (< 0.3, 0.3–0.5, 0.5–1.0, and > 1.0 g/g), with cutoff points determined based on clinical relevance and previous literature.[11]

The primary outcome was the change in eGFR over time, calculated using the CKD-EPI formula based on standardized serum creatinine measurements.[12] The stratification by baseline eGFR (15–60 vs ≥60 mL/min/1.73m²) was based on established clinical practice and previous studies showing different progression patterns in these groups. If patients developed eGFR < 15mL/min/1.73m^2, underwent kidney transplantation, hemodialysis, or peritoneal dialysis, or transferred to another center, these were considered to be censored events. The remaining patients were followed up until June 30, 2024.

Covariates at baseline included age, gender, systolic blood pressure (SBP), diastolic blood pressure (DBP), mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), tubular atrophy/interstitial fibrosis (T), and crescents (C) (known as the Oxford Classification MEST-C score system), selected based on their established associations with IgAN prognosis in previous studies.

Statistical Analysis

Continuous variables were presented as mean ± standard deviation for normally distributed data or median (interquartile range) for non-normally distributed data. Categorical variables were expressed as frequencies and percentages. Comparisons across TWAP categories were performed using one-way ANOVA or Kruskal–Wallis test for continuous variables, depending on their distribution. Chi-square test or Fisher's exact test was used for categorical variables.

We employed Generalized Additive Mixed Models (GAMMs)[13] to investigate the nonlinear associations between TWAP and longitudinal changes in eGFR. Patients were stratified into two groups based on their baseline renal function: 15 ≤ eGFR < 60 mL/min/1.73m² and eGFR≥60 mL/min/1.73m². The models were adjusted for age, gender, SBP, DBP,

and the Oxford Classification MEST-C markers. The initial eGFR was automatically included as a covariate in the GAMM method. Interaction terms between TWAP categories and time were incorporated to assess the impact of proteinuria levels on eGFR change rates over time. Effect estimates are presented as changes in eGFR (mL/min/1.73m²) per 1 standard deviation increment in the biomarker, along with 95% confidence intervals and P-values.

All statistical analyses were performed using the statistical software packages R (the R Foundation, Vienna, Austria), EmpowerStats (X&Y Solutions, Inc., Boston, MA, U.S.A)., and GraphPad Prism 8 (GraphPad Software Inc, La Jolla, CA, U.S.A)., and a two-tailed P-value < 0.05 was considered statistically significant.

Results

Baseline Characteristics and TWAP Stratification

Of the initial 1,244 patients screened, 695 were excluded for the following reasons: secondary IgAN (n = 15), missing follow-up data for protein-creatinine ratio or eGFR (n = 525), follow-up duration < 6 months (n = 123), and baseline eGFR < 15 mL/min/1.73m^2 (n = 32). The final study cohort consisted of 549 patients who met all inclusion criteria and had complete baseline and follow-up data. (Figure 1) Patients were stratified into four groups based on their time-weighted average proteinuria (TWAP) levels. Analysis of baseline characteristics across these groups revealed several statistically significant trends (P < 0.05) (Table 1).

With increasing TWAP levels, significant positive correlations were observed for body mass index (BMI), SBP and DBP. Metabolic parameters, including total cholesterol, triglycerides, and uric acid levels, also demonstrated significant upward trends. Conversely, hemoglobin, serum albumin, and IgG levels exhibited significant inverse correlations with increasing proteinuria. Notably, eGFR showed a marked decline across groups, with median values of 82.24, 81.70, 69.23, and 50.86 mL/min/1.73m² for the TWAP < 0.3, 0.3 to < 0.5, 0.5 to < 1, and ≥1 g/g groups, respectively. Baseline proteinuria/creatinine ratios displayed a significant progressive increase, with corresponding median values of 0.74, 1.19, 1.59, and 2.00 g/g across the aforementioned groups. Oxford classification analysis revealed a significant positive association between TWAP levels and the proportion of patients exhibiting tubular atrophy/interstitial fibrosis (T1/2) (P < 0.05).

Regarding treatment modalities, 39.16% of the patients received renin-angiotensin system inhibitors (RASi) alone, 35.15% received RASi in combination with corticosteroids/immunosuppressants (CSs/ISs), and 12.02% received CSs/ISs alone. Interestingly, the distribution of treatment modalities did not differ significantly among the TWAP groups (P > 0.05).

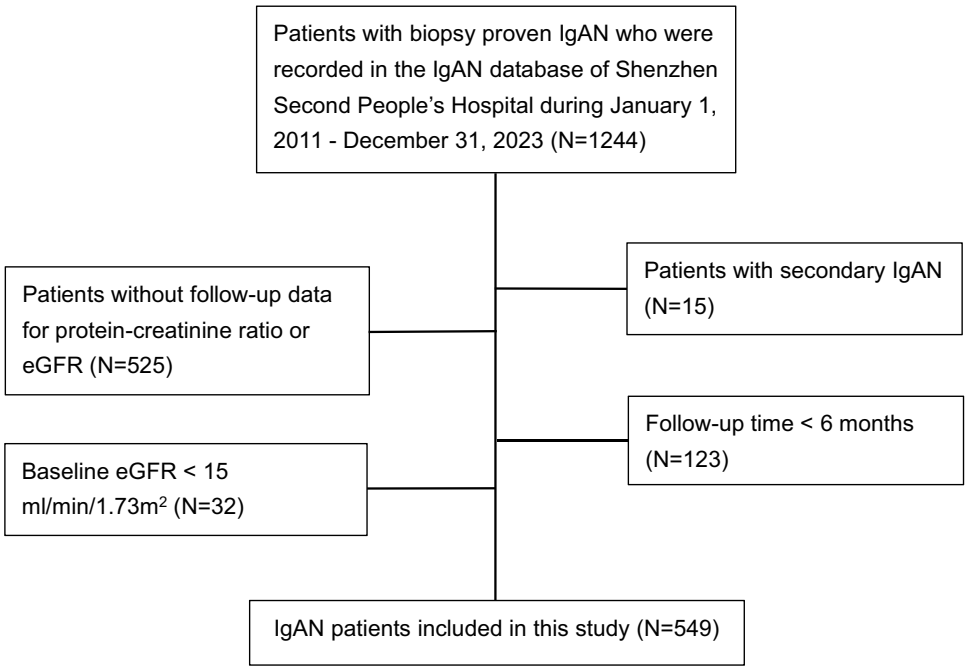

Figure 1 Flowchart of patients with immunoglobulin A nephropathy included in this study.

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Table 1 Baseline Characteristics According to Time-Weighted Average Proteinuria Category

Variables	Time-Weighted Average Proteinuria (g/g)				
	<0.3	0.3–0.5	0.5–1	≥1	P value
N	225	88	114	122	
Age, years	34.80 ± 9.21	37.07 ± 9.64	36.49 ± 10.71	37.48 ± 10.69	0.067
Male, n (%)	127 (56.44%)	43 (48.86%)	65 (57.02%)	56 (45.90%)	0.181
BMI, kg/m^2	22.26 ± 3.18	22.98 ± 3.11	23.19 ± 3.31	23.24 ± 3.70	0.026
SBP,mmHg	123.15 ± 15.62	126.30 ± 17.67	130.46 ± 21.16	137.37 ± 21.79	<0.001
DBP,mmHg	81.71 ± 11.73	82.92 ± 13.59	85.04 ± 14.18	90.17 ± 13.30	<0.001
Hemoglobin, g/L	131.55 ± 19.44	130.07 ± 17.72	129.05 ± 20.00	124.16 ± 20.13	0.009
Albumin, g/L	40.44 ± 4.82	39.47 ± 4.53	38.49 ± 4.80	36.35 ± 5.90	<0.001
Total cholesterol, mmol/L	4.79 ± 1.52	4.75 ± 1.01	4.99 ± 1.23	5.26 ± 1.58	0.022
Triglyceride, mmol/L	1.46 ± 1.19	1.44 ± 0.74	1.64 ± 1.19	1.91 ± 1.29	0.006
IgA, g/L	3.21 ± 1.07	3.06 ± 1.16	3.12 ± 0.93	3.04 ± 1.10	0.445
IgM, g/L	1.24 ± 0.60	1.26 ± 0.71	1.19 ± 0.55	1.28 ± 0.60	0.785
IgG, g/L	11.53 ± 2.87	10.58 ± 2.95	10.72 ± 2.99	9.74 ± 3.21	<0.001
Uric acid, umol/L	386.00 (323.00,455.00)	387.50 (306.00,469.00)	435.50 (332.75,503.50)	434.00 (371.25,544.25)	<0.001
eGFR, $mL/min/1.73m^2$	82.24 (67.01,101.17)	81.70 (54.16,99.26)	69.23 (51.98,95.52)	50.86 (32.05,84.33)	<0.001
Proteinuria/creatinine ratio, g/g	0.74 (0.45,1.29)	1.19 (0.77,1.76)	1.59 (0.85,2.47)	2.00 (1.07,3.80)	<0.001
Treatments, n (%)					
RASi alone, n (%)	93 (41.33%)	34 (38.64%)	43 (37.72%)	45 (36.89%)	0.871
RASi + CSs/ISs, n (%)	83 (36.89%)	29 (32.95%)	44 (38.60%)	37 (30.33%)	0.552
CSs/ISs alone, n (%)	23 (10.22%)	13 (14.77%)	13 (11.40%)	17 (13.93%)	0.585
Oxford Classification, n (%)					
Mesangial hypercellularity (M1)	185 (82.22%)	80 (90.91%)	84 (73.68%)	108 (88.52%)	0.008
Endocapillary hypercellularity (E1)	50 (22.22%)	25 (28.41%)	22 (19.30%)	29 (23.77%)	0.532
Segmental glomerulosclerosis (S1)	74 (32.89%)	36 (40.91%)	45 (39.47%)	56 (45.90%)	0.104
Tubular atrophy/interstitial fibrosis (T1/2)	42 (18.67%)	26 (29.55%)	46 (40.35%)	64 (52.46)	<0.001
Crescents (C1/2)	118 (52.44%)	57 (64.77%)	54 (47.37%)	73 (59.84%)	<0.001

Notes: data presented as mean ± SD, median (25th, 75th) or number (percent).
Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; IgA, Immunoglobulin A; eGFR, estimated glomerular filtration rate; BMI, body mass index; RASi, renin angiotensin system inhibitors; CSs/ISs, corticosteroids and (or) immunosuppressants.

TWAP and Longitudinal eGFR Changes

We employed Generalized Additive Mixed Models (GAMMs) to investigate the nonlinear associations between TWAP and longitudinal changes in eGFR, stratified by baseline renal function ($15 \leq eGFR < 60$ mL/min/1.73m² and eGFR ≥ 60 mL/min/1.73m²) (Table 2 and Figure 2). The median follow-up time was 27.06 months (interquartile range: 14.12–59.36 months). All models were adjusted for age, gender, SBP, DBP, and the Oxford Classification MEST-C markers.

In patients with $15 \leq eGFR < 60$ mL/min/1.73m², we observed a significant annual decline in eGFR of 3.07 mL/min/1.73m² (95% CI: −4.02 to −2.12, $P < 0.001$). The interaction between TWAP and time revealed that higher TWAP levels were associated with accelerated eGFR decline. Compared to patients with TWAP < 0.3 g/g, those with TWAP 0.3–0.5 g/g experienced an additional eGFR decline of 2.04 mL/min/1.73m² per year (95% CI: −3.72 to −0.35, $P = 0.018$). This decline was more pronounced in patients with TWAP 0.5–1 g/g and ≥ 1 g/g, with additional annual eGFR decreases of 3.38 mL/min/1.73m² (95% CI: −5.12 to −1.65, $P < 0.001$) and 4.04 mL/min/1.73m² (95% CI: −6.61 to −1.47, $P = 0.002$), respectively. In patients with eGFR ≥ 60 mL/min/1.73m², the average annual eGFR decline was 1.64 mL/min/1.73m² (95% CI: −2.09 to −1.19, $P < 0.001$). A significant interaction was observed only between TWAP ≥ 1 g/d and time ($\beta = -5.70$, 95% CI: −6.84 to −4.55, $P < 0.001$), indicating that patients with high proteinuria experienced an additional eGFR decline of 5.70 mL/min/1.73m² per year compared to those with TWAP < 0.3 g/g.

Table 2 Association of the Time-Weighted Average Proteinuria With the Changes in Renal Function According to 15 ≤ eGFR < 60 and eGFR ≥ 60 mL/min/1.73m^2

Variable	15 ≤ eGFR < 60 mL/min/1.73m²		eGFR ≥ 60 mL/min/1.73m²	
	Beta (95% CI)	P value	Beta (95% CI)	P value
Time, year	−3.07 (−4.02 to −2.12)	<0.001	−1.64 (−2.09 to −1.19)	<0.001
Time-weighted average proteinuria (TWAP, g/g)				
<0.3	reference		reference	
0.3–0.5	−5.10 (−13.01 to 2.81)	0.208	−1.69 (−8.07 to 4.68)	0.603
0.5–1	−8.93 (−16.20 to −1.66)	0.017	−0.85 (−6.79 to 5.09)	0.78
≥1	−16.98 (−23.78 to −10.18)	<0.001	−0.93 (−8.02 to 6.15)	0.796
Time×TWAP (g/g)				
Time×TWAP (<0.3)	reference		reference	
Time×TWAP (0.3–0.5)	−2.04 (−3.72 to −0.35)	0.018	−0.04 (−1.98 to 1.89)	0.964
Time×TWAP (0.5–1)	−3.38 (−5.12 to −1.65)	<0.001	0.52 (−0.48 to 1.52)	0.311
Time×TWAP (≥1)	−4.04 (−6.61 to −1.47)	0.002	−5.70 (−6.84 to −4.55)	<0.001

Notes: Generalized additive mixed models (GAMMs) were used to investigate the nonlinear fixed effects of TWAP associations with the longitudinal changes in eGFR in patients with 15 ≤ eGFR < 60mL/min/1.73m² and eGFR ≥ 60mL/min/1.73m², respectively. Estimates are in mL/min/1.73m2 per 1 SD increment in biomarker.In the GAMMs, TWAP and Time×TWAP (Time-TWAP interaction) were adjusted for age, gender, SBP, DBP, the Oxford Classification MEST-C markers (GAMM method included the initial eGFR as a covariate automatically).
Abbreviation: Time-weighted average proteinuria, TWAP.

Discussion

Various approaches have been developed to quantify proteinuria exposure in IgAN. These methods primarily include baseline proteinuria, time-averaged proteinuria (TAP), and time-varying proteinuria (TVP), or these indicators standardized to body surface area, each with distinct methodological considerations.[14] While baseline proteinuria provides important initial clinical information, it fails to capture the dynamic nature of protein excretion throughout disease progression. TAP, calculated as the arithmetic mean of measurements over time, has been extensively validated.[15,16] However, TAP's accuracy may be compromised by irregular sampling intervals and proteinuria fluctuations between measurements. Recent studies have explored TVP as an alternative approach, offering valuable insights through multiple time-point analysis.[17] While TVP methodology improves upon baseline measurements, it assigns equal weight to each measurement regardless of inter-assessment intervals, potentially limiting its ability to fully capture temporal patterns of proteinuria exposure. The significance of time-weighted approaches in tracking proteinuria has been demonstrated across various kidney diseases. Notably, Groop et al conducted a randomized controlled trial in diabetes research, employing time-weighted mean albuminuria, a concept analogous to our TWAP, which effectively demonstrated the utility of temporal weighting in assessing proteinuria progression.[10] Their findings underscore the broader applicability of time-weighted methodologies beyond traditional remission targets. In this context, our study investigated TWAP as a complementary method to existing approaches. TWAP addresses several limitations of previous methods by accounting for irregular follow-up intervals common in clinical settings and incorporating temporal weighting to reflect both duration and magnitude of proteinuria exposure. This approach was developed based on the hypothesis that tissue damage in IgAN relates to cumulative proteinuria exposure over time.[18]

Our single-center retrospective cohort study of 549 IgAN patients revealed significant associations between elevated TWAP levels and eGFR decline, particularly in patients with moderate to severe renal impairment (15 ≤ eGFR < 60 mL/min/1.73m²). These patients showed progressively greater annual eGFR declines with increasing TWAP levels: 2.04 mL/min/1.73m² for TWAP 0.3–0.5 g/g (95% CI: −3.72 to −0.35), 3.38 mL/min/1.73m² for TWAP 0.5–1 g/g (95% CI: −5.12 to −1.65), and 4.04 mL/min/1.73m² for TWAP ≥1 g/g (95% CI: −6.61 to −1.47). In patients with an eGFR ≥ 60 mL/min/1.73m², a significant eGFR decline was observed only at TWAP ≥1 g/g, with an additional annual decrease of 5.70 mL/min/1.73m² (95% CI: −6.84 to −4.55). To validate our findings, we performed additional analyses adjusting for various treatment regimens (RASi alone, RASi with CSs/ISs combination, and CSs/ISs monotherapy). The consistency of results across these analyses suggests that the TWAP-eGFR decline association may be independent of treatment strategies.

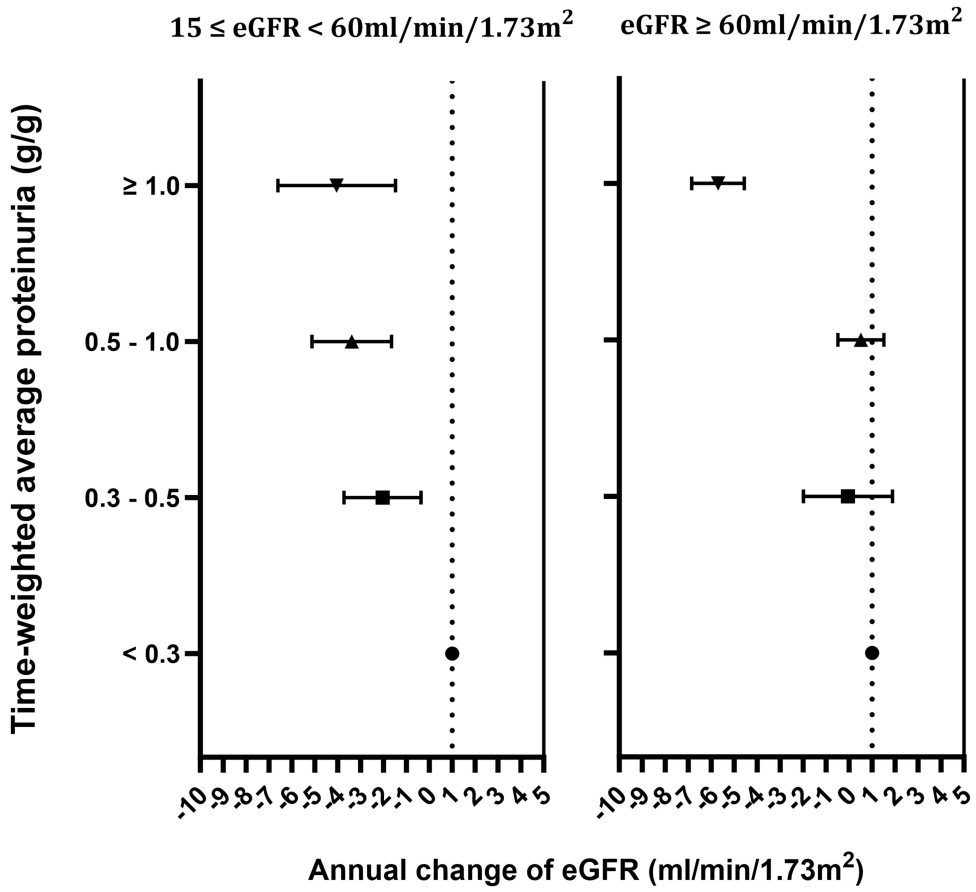

Figure 2 Association of time-weighted average proteinuria with the annual changes in estimated glomerular filtration rate (eGFR) in IgAN patients.The data presented in this figure are derived from Table 2. The graph illustrates the comparative eGFR changes across different TWAP groups, with TWAP<0.3 g/g serving as the reference group. The values displayed for other TWAP categories represent the additional annual eGFR changes relative to the reference group, stratified by baseline renal function (eGFR ≥60 mL/min/1.73m² and 15–60 mL/min/1.73m²) in IgA nephropathy patients.

Our findings align with and extend previous research on proteinuria management in IgAN. Through a longitudinal cohort analysis, Reich et al[6] demonstrated improved prognosis with proteinuria remission. The UK RaDaR registry study of 2,299 adults and 140 children (proteinuria > 0.5 g/day or eGFR < 60 mL/min/1.73m2) employed time-average proteinuria measurements and showed that maintaining levels below 0.44 g/g was associated with slower eGFR decline and improved survival.[16] Similarly, Le et al's observational study of 1,155 Chinese IgAN patients using time-average proteinuria established sustained proteinuria as a strong predictor of renal failure, recommending targets of < 1.0 g/day (basic) and < 0.5 g/day (optimal).[15] Tang et al[17] utilized time-varying proteinuria measurements with marginal structural models, revealing a graded relationship between proteinuria and renal outcomes, particularly noting significant variance below 0.5 g/d. The threshold effects observed in our study align with Wyatt et al's[19] pathophysiological perspective suggesting buffering mechanisms against moderate proteinuria, which may become overwhelmed at higher levels. These diverse studies, despite methodological variations, consistently support that lower proteinuria levels reduce kidney failure risk. Our study extends this consensus by proposing lower thresholds through the TWAP approach, potentially offering enhanced protection against renal function decline, particularly in high-risk populations.

The clinical significance of our study lies in its potential to enhance IgAN management through the novel TWAP assessment method. This approach provides a more nuanced understanding of long-term proteinuria exposure and its relationship with renal function decline. Our findings suggest benefits from maintaining TWAP below 0.3 g/g, particularly in patients with existing renal dysfunction, supporting earlier and more aggressive proteinuria reduction strategies.

Several limitations warrant consideration. As a single-center retrospective study with a predominantly Chinese cohort, our findings have limited generalizability. The observational design precludes causal inference, and unmeasured

confounders may impact results. Additionally, our study did not directly compare different proteinuria assessment methods, and strict inclusion criteria may affect broader clinical applicability.

In conclusion, our study demonstrates the utility of TWAP as a predictor of renal function decline in IgAN, suggesting that maintaining TWAP below 0.3 g/g may significantly slow disease progression, particularly in patients with moderate to severe renal impairment. Future research should focus on validating these findings in diverse populations and comparing various proteinuria measurement techniques to optimize risk stratification and treatment monitoring in IgAN.

Data Sharing Statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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