

## CLINICAL OUTCOMES OF HEMATURIA IN CHILDREN: SINGLE-CENTER EXPERIENCE

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### Abstract

**Introduction:** Hematuria in children is common and may be transient or benign, but persistent cases can signal glomerular disease or structural abnormalities. It is increasingly recognized as a risk factor for chronic kidney disease, as ongoing hematuria may contribute to renal injury.

Careful evaluation and long-term follow-up are essential to distinguish benign cases from those at risk of progression, with genetic testing and early treatment helping to improve outcomes.

**Objectives:** The objective of this study was to evaluate the clinical outcomes of children presenting with hematuria, with particular focus on the persistence of hematuria, proteinuria, and changes in estimated glomerular filtration rate (eGFR) over time.

**Material and methods:** The study, conducted between 2018 and 2022 at the University Children's Hospital in Skopje, included children with confirmed hematuria. The diagnostic workup comprised detailed family history, physical examination, ultrasound of the urinary tract and laboratory investigations. Clinical outcomes were assessed by monitoring urinary abnormalities and evaluating renal function through eGFR.

**Results:** Of 441 children with hematuria, 317 (72%) had microhematuria and 124 (28%) had macrohematuria. Follow-up was conducted in 174 patients (39.4%), with a mean duration of  $27.51 \pm 23.84$  months and a median of 20 months. There was a statistically significant difference between eGFR1 and eGFR2 ( $p < 0.001$ ). On average, eGFR values increased markedly from the first visit (mean =  $74.73 \text{ ml/min/1.73m}^2$ ) to the follow-up visit (mean =  $99.05 \text{ ml/min/1.73m}^2$ ), indicating substantial improvement in renal function over time.

There was significant association between etiology and long-term kidney outcome ( $p=0.0003$ ). Patients with COL4 related nephropathy and glomerulonephritis were more likely to develop impaired renal outcomes compared to APSGN or pyelonephritis. During follow-up, hematuria persisted in 49 patients (28%), mostly microscopic, with only three macroscopic cases.

Proteinuria was present in 20 (14%), including 4 with nephrotic-range levels. Eight developed CKD stages 2–5, and eight progressed to end-stage renal failure; six received transplants, while two remained on dialysis. Three patients (0.7%) died, all with severe underlying disease.

**Conclusion:** outcomes of hematuria in children is largely determined by etiology. Most children recover renal function, but those with glomerular or genetic disorders face higher risk of CKD and ESRD. Early etiologic classification and monitoring of proteinuria are critical for identifying patients who require intensive long-term follow-up

**Key words:** hematuria, macroscopic, microscopic, children, outcome.

## **Introduction**

Hematuria in children is a relatively common clinical finding that can be either macroscopic or microscopic in form. Whereas the majority of them are transient and benign, for example, due to fever, heavy exercise, or urinary infection, persistent or recurrent hematuria may suggest serious underlying conditions such as glomerular diseases-IgA nephropathy, Alport syndrome-or structural abnormalities of the urinary tract. [1,2]

Whereas hematuria has conventionally been regarded as a benign finding in glomerular diseases, there is an increasing recognition nowadays that it is indeed an independent risk factor for progression of CKD. Both experimental and clinical evidence points to the role of persistent hematuria in promoting renal injury through mechanisms such as oxidative stress, tubular damage, and inflammatory responses related to the lysis of red blood cells within the urinary tract. In IgA nephropathy and other glomerulopathies, the occurrence and persistence of hematuria relate to worse renal outcomes, including a more rapid decline in GFR and higher risk of progressing to ESKD. [3].

Urinary screening programs in children have proven to be an important public health measure for the early detection of renal abnormalities, particularly hematuria, which may otherwise remain clinically silent. Large-scale school-based screening initiatives have demonstrated that routine urine testing can uncover asymptomatic hematuria and proteinuria at an early stage, allowing clinicians to distinguish between benign, transient findings and those suggestive of progressive glomerular disease.

By identifying these children early, screening programs enable timely referral, closer monitoring, and targeted interventions that can alter the disease trajectory and reduce long-term morbidity. [4, 5, 6, 7].

Careful evaluation, including urine microscopy, assessment for proteinuria, blood pressure monitoring, and imaging when indicated, is essential to distinguish benign from pathological causes. Isolated microscopic hematuria without proteinuria, hypertension, or impaired renal function is usually benign and carries an excellent prognosis, often resolving spontaneously or remaining stable without progression. In contrast, hematuria associated with glomerular diseases such as IgA nephropathy or Alport syndrome may evolve into proteinuria and chronic kidney disease, with some patients progressing to end-stage renal disease if not closely monitored.

Post-infectious glomerulonephritis generally has a favorable outcome, though microscopic hematuria may persist for months, while thin basement membrane nephropathy typically remains benign throughout life. [8, 9]

Nowadays, genetic studies show that even microscopic hematuria can carry a real risk of progressive kidney disease, with long-term data revealing an increased incidence of end-stage kidney disease even in seemingly mild cases. Therefore, family screening and genetic testing for accurate diagnosis and prognosis are very important, since early diagnosis and early treatment with renin-angiotensin blockers can help slow the progression of the disease in affected patients. [10, 11, 12, 13, 14]

Thus, careful evaluation and long-term follow-up are essential to distinguish transient cases from those with significant renal pathology and to optimize outcomes.

## **Objectives**

The objective of this study was to evaluate the clinical outcomes of children presenting with hematuria, with particular focus on the persistence of hematuria, proteinuria, and changes in estimated glomerular filtration rate (eGFR) over time. By monitoring these parameters, the study aimed to identify patterns of renal function recovery or deterioration, assess the risk of progression to chronic kidney disease.

## **Material and methods**

The study includes 441 children with confirmed hematuria in the period 2108- 2022, at the University Children's Hospital – Skopje. Workup of patients includes a detailed family history of kidney disease in the family and other hereditary diseases.

Then a detailed physical examination, with measurement of body weight and arterial blood pressure and ultrasound examination of the urinary tract. Laboratory studies include biochemical tests to define the

etiology of hematuria. The clinical outcome of hematuria was evaluated by monitoring urinary abnormalities and assessing renal function through eGFR.

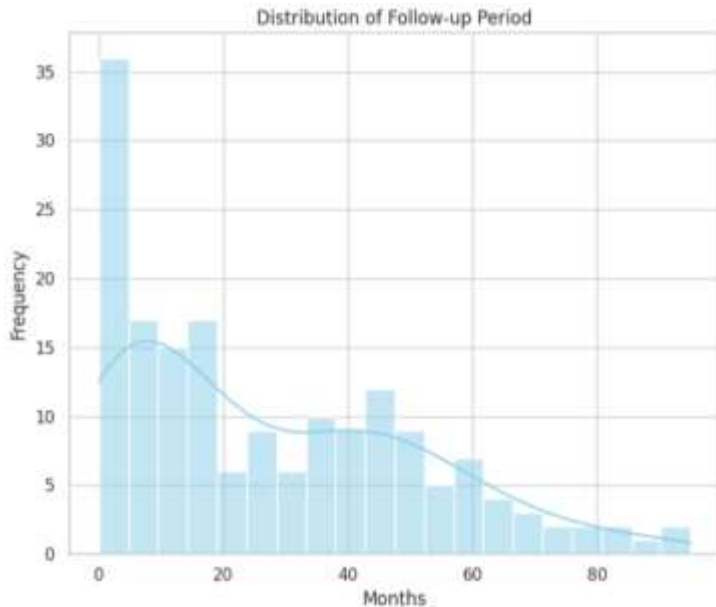
Statistical analysis was performed to evaluate changes in renal function over time. Descriptive statistics (mean, median, standard deviation, and range) were calculated for baseline eGFR (eGFR1) and follow-up eGFR (eGFR2).

The Wilcoxon Signed-Rank Test was applied to compare paired eGFR values, given the non-parametric distribution of the data. In addition, changes in eGFR ( $\Delta$ eGFR) were analyzed across different etiological groups, with group-wise averages and medians reported. Graphical methods, including boxplots and histograms, were used to illustrate the distribution of eGFR values and changes by etiology. A Chi-Square test of independence was performed to examine the relation between etiology and long-term kidney outcome.

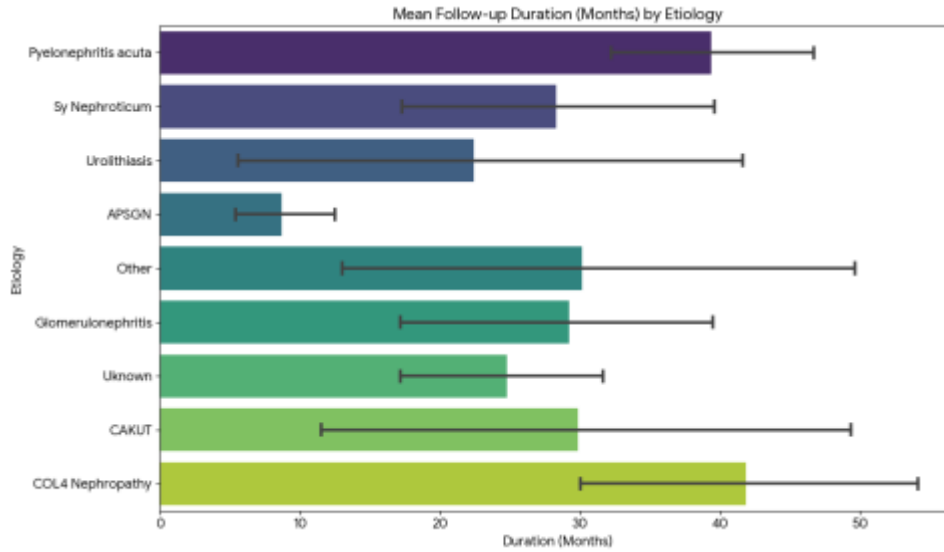
## Results

A total of 441 children with hematuria was examined, of whom 317 (72%) had microhematuria and 124 (28%) had macrohematuria. The gender distribution of the participants consisted of 212 (48%) male patients and 229 (52%) female patients.

The follow-up of hematuria was analyzed in 174 of 441 patients (39.4%), with follow-up durations ranging from 0 to 95 months (nearly 8 years), yielding a mean of  $27.51 \pm 23.84$  months and a median of 20 months, which indicates an asymmetric distribution skewed toward shorter follow-up periods; quartile analysis showed that 25% of patients were followed for 7 months or less, while 75% had follow-up of up to 44 months, and diagnosis-specific differences were evident, as patients with acute pyelonephritis and COL4-associated nephropathy had longer average follow-up periods of about 42 months, whereas those with acute post-streptococcal glomerulonephritis were monitored for a significantly shorter average of 8.7 months.



**Figure 1.** – Distribution of follow-up duration



**Figure 2.** – Follow-up duration by etiology

During follow-up, hematuria persisted in 49 of 174 patients (28%), in all cases being microscopic with varying intensity, while only three patients’ macroscopic hematuria persisted. Proteinuria persisted in 20 of 174 patients (14%), with 16 showing moderate levels and 4 presenting proteinuria of nephrotic range. Over the course of follow-up, eight children were categorized as having chronic kidney disease stages 2 to 5 (CKD 2–5), and eight progressed to end-stage renal failure, of whom six underwent kidney transplantation, one remained on hemodialysis, and one on peritoneal dialysis.

Three children died (0.7%), all with severe pathology: one with hemolytic uremic syndrome who died in the acute phase, one girl with systemic lupus erythematosus who died in the stage of end-stage renal failure while on hemodialysis, and one girl with a transplanted kidney who died from sepsis following the second transplantation.

The analysis of the estimated glomerular filtration rate (eGFR) showed a significant increase during the follow-up period. At baseline (eGFR1), the mean value was 74.73 ml/min/1.73 m<sup>2</sup>, with only 32.2% of patients having a “normal/high” eGFR ( $\geq 90$  ml/min/1.73 m<sup>2</sup>).

During follow-up (eGFR2), the mean value increased to 99.05 ml/min/1.73 m<sup>2</sup>. The proportion of patients with “normal/high” eGFR rose to 69.2%, while the percentage of patients with significantly reduced kidney function dropped from 25.7% to 2.8%.

**Table 1.** - eGFR at baseline and during follow-up

	eGFR1 (ml/min/1.73m <sup>2</sup> )	eGFR2 (ml/min/1.73m <sup>2</sup> )
Mean	74.73	99.05
Std. Deviation	27.86	21.89

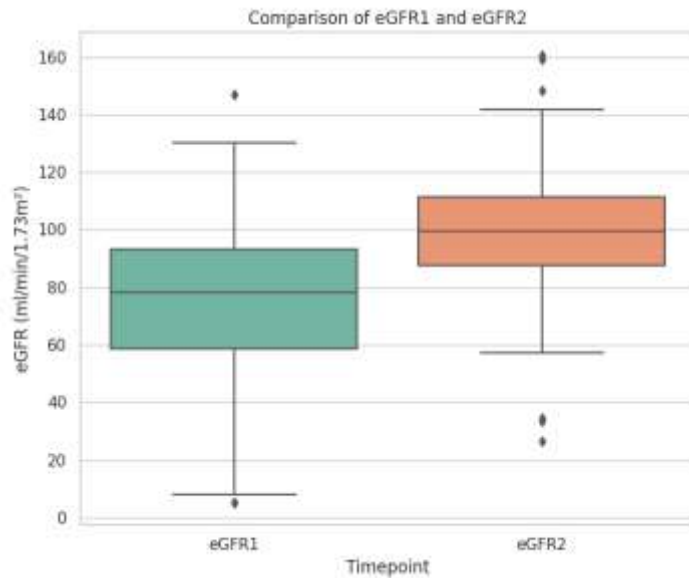
**Table 2.** – Distribution of patients by eGFR category during follow-up

eGFR category	Basal (eGFR1)	Follow-up (eGFR2)
Normal/high ( $\geq 90$ )	32.2%	69.2%
Mildly decreased (60-89)	42.1%	28.0%
Decreased ( $< 60$ )	25.7%	2.8%

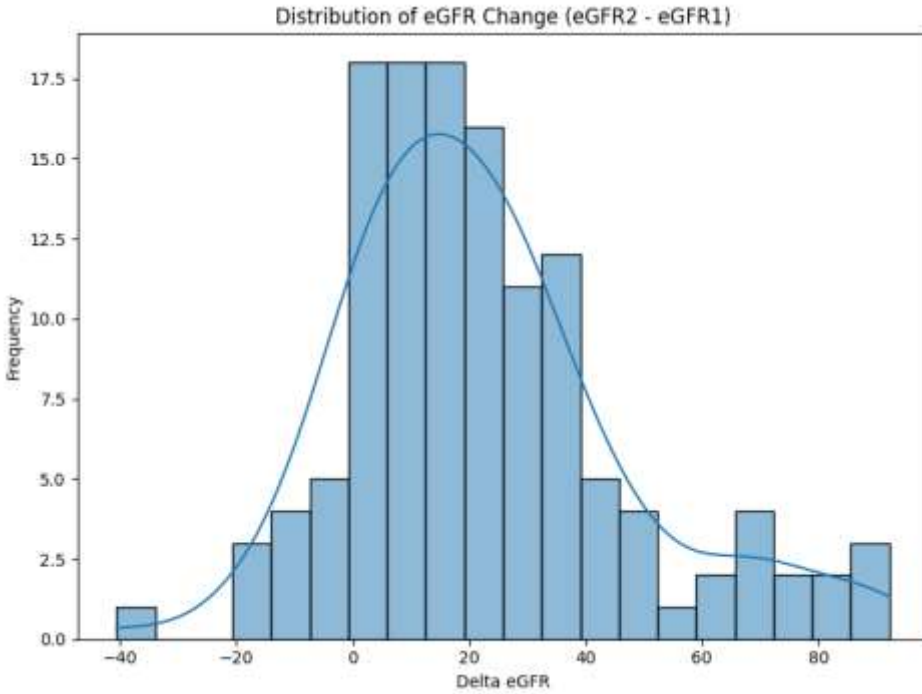
There was a statistically significant difference between eGFR1 and eGFR2 ( $p < 0.001$ ). On average, eGFR values increased markedly from the first visit (mean = 74.73 ml/min/1.73m<sup>2</sup>) to the follow-up visit (mean = 99.05 ml/min/1.73m<sup>2</sup>), indicating substantial improvement in renal function over time.

The mean improvement per patient was +22.32 ml/min/1.73m<sup>2</sup>, with a median change of +18.1 ml/min/1.73m<sup>2</sup> and a wide range from -40.6 to +92.2 ml/min/1.73m<sup>2</sup>. In 75% of patients, an improvement of at least +6.2 ml/min/1.73m<sup>2</sup> was observed. A statistically significant positive correlation was found between the duration of follow-up and the degree of eGFR change ( $r = 0.380$ ;  $p = 0.000$ ).

The greatest average improvement in eGFR was recorded in patients with acute pyelonephritis (+27.76 ml/min/1.73m<sup>2</sup>) and acute post-streptococcal glomerulonephritis (+24 ml/min/1.73m<sup>2</sup>), while more moderate changes were noted in patients with nephrotic syndrome and in cases of unknown etiology, ranging from approximately +10 to +11 ml/min/1.73m<sup>2</sup>.

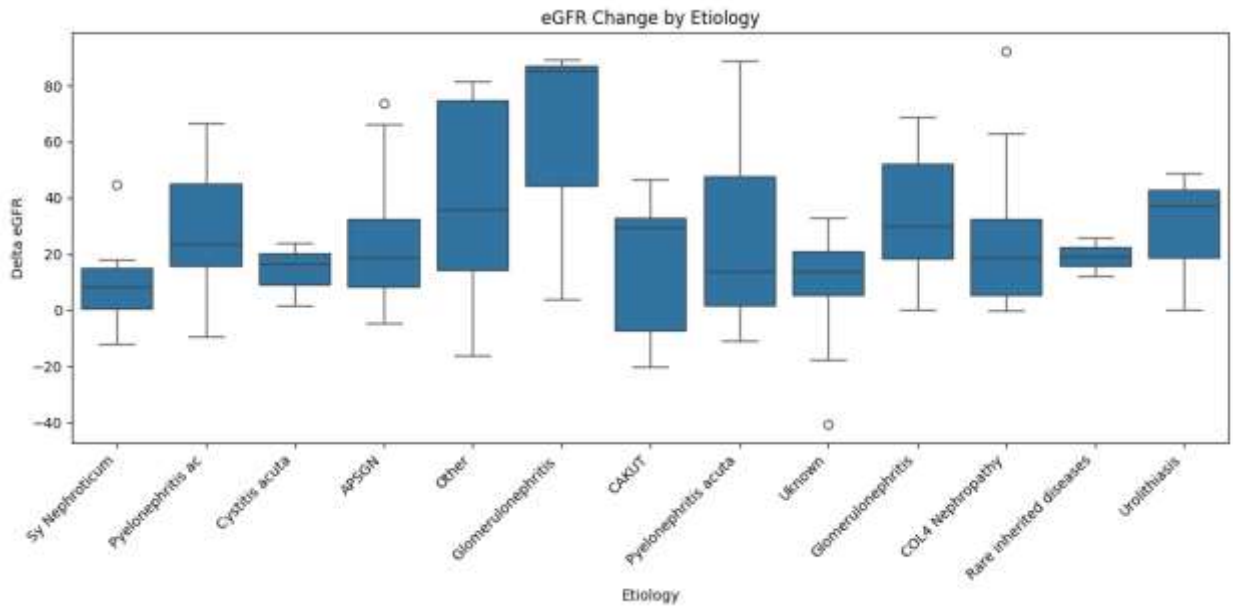


**Figure 3.** – Comparison of eGFR during follow-up (Wilcoxon Signed-Rank Test;  $p < 0.001$ ).



**Figure 4.** – Distribution of eGFR change.

In the total patient group, the change in eGFR during follow-up was also analyzed according to the etiology of hematuria, which showed that patients with acute pyelonephritis and acute post-streptococcal glomerulonephritis demonstrated the greatest improvement in renal function compared to other etiologies. So, the etiology of hematuria strongly influences the degree of renal function improvement over time.



**Figure 5.** – eGFR change by etiology of hematuria

A Chi-Square test of independence was performed to examine the relation between etiology and long-term kidney outcome. The relation between these variables was significant,  $\chi^2(8, N=157)=29.17, p=.0003$ . Patients with COL4 related nephropathy and glomerulonephritis were significantly more likely to have impaired kidney outcomes compared to those with APSGN or pyelonephritis.

Fisher's Exact Test, confirmed that patients with glomerulonephritis were significantly more likely to progress to impaired renal status compared to the APSGN cohort ( $p=0.016$ ). COL4 related nephropathy also demonstrated a strong clinical trend toward impairment ( $p=0.059$ ).

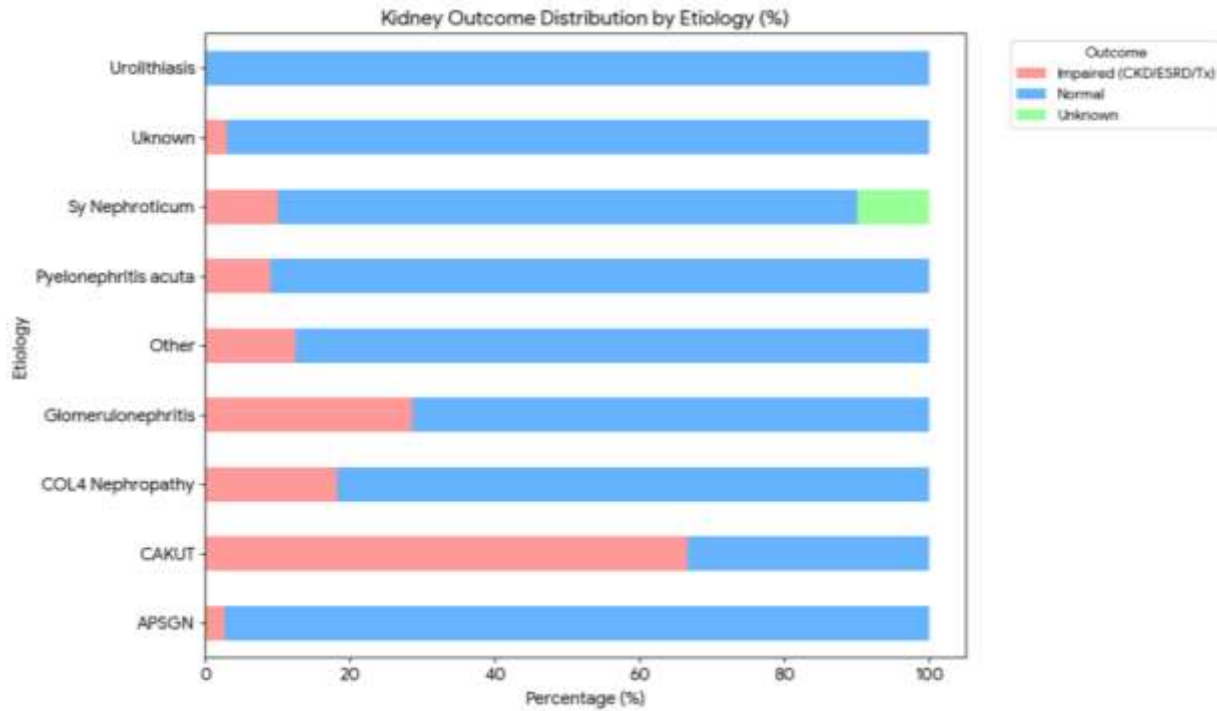


Figure 6. – Kidney Outcome Distribution by Etiology.

### Discussion

The clinical management of pediatric hematuria remains a challenge due to the diverse range of underlying etiologies. Our study analyzed the renal outcomes of a large cohort, focusing on the evolution of the estimated glomerular filtration rate (eGFR) and the predictive value of etiology on patient prognosis.

#### Renal Function Recovery and eGFR Dynamics

One of the most important findings in this study was the significant overall improvement in renal function observed from baseline to follow-up. The mean eGFR rose from 74.73 to 99.05 ml/min/1.73m<sup>2</sup>, with the proportion of patients having "normal" kidney function increasing from 32.2% to 69.2%.

This marked improvement is largely driven by the high prevalence of acute inflammatory conditions in the cohort, such as acute post-streptococcal glomerulonephritis (APSGN) and acute pyelonephritis. In these cases, the initial low eGFR likely reflects an episode of acute kidney injury that resolves as the underlying infection or inflammation subsides.

### Etiology as a Predictor of Adverse Outcomes

Despite the general trend toward recovery, our analysis using the Chi-Square test ( $p=0.0003$ ) and Fisher's Exact Test identified etiology as the most critical predictor of long-term impairment.

While acute conditions showed favorable recovery, chronic glomerular diseases presented a vastly different trajectory.

Patients with glomerulonephritis were significantly more likely to progress to impaired renal status compared to those with APSGN ( $p=0.016$ ). Similarly, COL4-associated nephropathy (including Alport Syndrome) demonstrated a strong clinical trend toward impairment ( $p=0.059$ ).

Pathophysiological, these conditions are characterized by permanent structural damage to the glomerular basement membrane, unlike the transient immune-complex deposition seen in APSGN. The persistence of proteinuria in 14% of the cohort further serves as a "red flag" for these patients, as proteinuria is a well-established independent risk factor for the progression toward ESRD.

### The Role of Monitoring

The study also highlighted significant disparities in clinical management. Patients with chronic or genetic etiologies (COL4, Glomerulonephritis) were monitored for significantly longer periods (median ~42 months) compared to those with APSGN (median ~8.7 months). This reflects a stratified approach to pediatric nephrology: acute cases require intensive short-term monitoring until resolution, whereas chronic cases require a lifelong "renal preservation" strategy.

### Limitations of the study

While the study provides robust longitudinal data, it is limited by the single-center nature of the data and the loss to follow-up of a portion of the original cohort. Furthermore, the wide range of eGFR changes (from -40.6 to +92.2) underscores the high inter-individual variability in renal recovery.

Comparing our results to reported literature, our cohort aligns with the broader consensus that pediatric hematuria outcomes are bifurcated by etiology, though our study demonstrates a notably high eGFR recovery rate. While global literature on APSGN consistently reports an "excellent" short-term prognosis with over 85–90% renal recovery, studies from tertiary centers in developing regions show a lower recovery rate of ~85% with 15% progressing to CKD.

Furthermore, our findings regarding COL4-associated nephropathy and chronic glomerulonephritis mirror the NAPRTCS and CKiD registry data, which identify primary glomerular disease and persistent proteinuria as the most potent non-modifiable risk factors for progression, with glomerular etiologies having a significantly higher hazard ratio (HR 2.59) for decline compared to non-glomerular causes.

This reinforces our conclusion that while the "infectious-inflammatory" majority drives the overall positive trend, the "structural-genetic" minority requires a distinct, lifelong renal preservation strategy. [15, 16, 17].

### Conclusion

In conclusion, the etiology of pediatric hematuria is the primary determinant of long-term kidney health. While the majority of children exhibit significant renal recovery, those with underlying glomerular or genetic pathologies remain at high risk for progression to CKD and ESRD.

Early etiologic classification and the monitoring of persistent proteinuria are essential to identifying high-risk patients who require aggressive long-term renal surveillance.

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