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Risk Factors for Kidney Impairment in Pediatric Nephrolithiasis and Nephrocalcinosis: A Single-Center Experience

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Abstract

Background: In recent decades, nephrolithiasis (NL) and nephrocalcinosis (NC) have been increasingly recognized as significant public health concerns in the pediatric population, with reported increases of up to 10% in various countries. Both conditions are associated with an increased risk of kidney impairment and progression to chronic kidney disease (CKD). However, the factors contributing to kidney dysfunction and their impact on kidney outcomes in affected children remain incompletely understood.

Methods: We conducted an ambispective observational study that included 176 pediatric patients diagnosed with nephrolithiasis, nephrocalcinosis, or microlithiasis at a single center. Metabolic abnormalities (hypercalciuria, hyperoxaluria, hyperuricosuria, and hypocitraturia), family history, genetic mutations, and ultrasound findings were analyzed. Kidney function was assessed using the estimated glomerular filtration rate (GFR). Associations between potential risk factors and reduced GFR were evaluated using statistical analysis, including logistic regression.

Results: Reduced GFR was significantly associated with hypercalciuria ($p=0.022$), hyperoxaluria ($p=0.035$), and genetic mutations ($p<0.001$). Compared with nephrolithiasis and microlithiasis, nephrocalcinosis was strongly associated with impaired kidney function, with a significantly higher prevalence of reduced GFR ($p=0.004$). Younger age was also associated with increased risk, while increasing age had a protective effect. Multivariate analysis revealed that genetic mutations remained the strongest independent predictor of kidney injury. The risk of CKD progression increased with the accumulation of multiple risk factors.

Conclusions: Genetic mutations, hypercalciuria, hyperoxaluria, younger age, and nephrocalcinosis are key risk factors for kidney damage in pediatric urolithiasis patients. The early identification of high-risk patients is essential for preventing disease progression and optimizing long-term kidney outcomes.

Clinical trial registration

Not applicable

Keywords: Pediatric nephrolithiasis; Nephrocalcinosis; Kidney impairment; Metabolic factors; Genetic mutations; Risk factors

Introduction

Nephrolithiasis (NL) and nephrocalcinosis (NC) are being increasingly observed in the pediatric population and represent important causes of kidney morbidity [1]. In recent decades, NL and NC have become increasingly recognized as important public health concerns in the pediatric population, with reported increases of up to 10% in various countries [2-6]. The exact prevalence in the pediatric population remains unclear because of limited epidemiological data.

Nephrolithiasis is a systemic metabolic disorder characterized by the formation of calculi within the urinary tract, while nephrocalcinosis refers to diffuse calcium deposition in the renal parenchyma, most commonly involving the renal medulla. Although these conditions are closely related, they differ in their pathophysiology, clinical presentation, and prognosis [7, 8]. NC typically presents early in life and is almost always associated with an underlying metabolic or genetic disorder, whereas NL may also occur in otherwise healthy individuals. Importantly, NC may not cause symptoms for prolonged periods but is associated with a significant risk of progression to chronic kidney disease (CKD); in contrast, NL often causes symptoms; however, those symptoms do not always reflect disease severity [9]. Microlithiasis (ML) is defined as the presence of hyperechogenic structures <3 mm within the renal calyces, pelvis, or ureter detected by ultrasonography [10, 11]. The prevalence of ML among children may be as high as 60%, although its clinical significance and prognosis remain unclear [12].

The etiology of pediatric nephrolithiasis has shifted in recent decades, with metabolic abnormalities now representing the predominant cause. Metabolic factors are identified in approximately 70–80% of cases, with hypercalciuria being the most

common lithogenic factor, followed by hypocitraturia, hyperoxaluria, and hyperuricosuria [13-15]. A positive family history is reported in up to 40% of patients, and monogenic disorders account for 10–20% of cases, highlighting the important role of genetic predisposition [16, 17]. Among metabolic factors, hypercalciuria is the most significant risk factor for stone formation and recurrence and is often associated with familial predisposition and early disease onset. Hypocitraturia contributes to lithogenesis by reducing the urinary inhibition of calcium crystallization, while hyperoxaluria and hyperuricosuria further promote stone formation through increased urinary supersaturation and altered physicochemical balance [15, 18]. ML is frequently associated with metabolic abnormalities such as those observed in nephrolithiasis and may represent an early stage of stone formation. Therefore, children with ultrasound-detected ML require careful follow-up to prevent progression and complications [19].

Both NL and NC are associated with an increased risk of kidney impairment. The mechanisms underlying progression to CKD include chronic tubular injury due to calcium deposition, recurrent obstructive events, infections, and the impact of underlying genetic disorders [20-22]. Patients with nephrolithiasis have an approximately twofold greater risk of developing CKD than the general population does. Despite these observations, the factors associated with kidney damage in pediatric patients remain incompletely understood [23]. In particular, the relative contribution of metabolic abnormalities, genetic factors, and ultrasound findings to renal outcomes requires further clarification. Therefore, the aim of the present study was to identify, in a single-center cohort, risk factors for kidney injury in children with nephrolithiasis and nephrocalcinosis and to evaluate their impact on kidney function.

Methods

Study design

An ambispective observational study was conducted at the Specialized Hospital for Active Treatment of Children's Diseases "Prof. Ivan Mitev" in Sofia, Bulgaria, and included pediatric patients diagnosed with microlithiasis, nephrolithiasis and nephrocalcinosis. A total of 176 children were included in the study. Diagnosis was established based on ultrasound findings. Clinical, laboratory, and imaging data were collected from medical records. The following variables were analyzed: age at presentation, sex, family history, metabolic abnormalities and ultrasound findings, estimated glomerular filtration rate (eGFR) and genetic testing results.

Clinical and laboratory assessments

A detailed family history was obtained for all patients. Metabolic evaluation included assessments of hypercalciuria, hyperoxaluria, hyperuricosuria, and hypocitraturia. The metabolic assessment for calciuria was performed using 24-hour urine collection, which is considered the gold standard for evaluating urinary metabolites and electrolytes. The adequacy of urine collection was verified by urinary creatinine excretion, with expected values of 0.10–0.30 mmol/kg/24 h. Values outside that range suggested incomplete or inaccurate collection. For patients unable to complete a 24-hour collection, the spot urine calcium-to-creatinine ratio (Ca/Cr) was used as an alternative method. Citrate excretion was available for 70 patients, oxalate excretion was available for 68 patients,

and uric acid excretion was available for 129 patients. A major limitation of the analysis of these metabolites is incomplete data availability due primarily to two factors: first, their assessment requires 24-hour urine collection, which is not feasible for all pediatric patients; second, citrate and oxalate measurements are not routinely performed at our institution and must be conducted at external laboratories at the patients' expense. Genetic testing was performed for selected patients with suspected hereditary forms of the disease.

Renal function assessment

Renal function was evaluated using the eGFR, which was calculated according to the modified Schwartz formula (2007), an updated version of the original Schwartz equation (1976) that incorporates age- and sex-specific coefficients for improved accuracy in pediatric populations. Patients were categorized according to the KDIGO classification for CKD: G5 (severe CKD, <15 mL/min/1.73 m²), G4 (15–29 mL/min/1.73 m²), G3 (30–59 mL/min/1.73 m²), G2 (60–89 mL/min/1.73 m²), G1 (90–119 mL/min/1.73 m²), and hyperfiltration (≥120 mL/min/1.73 m²). Reduced kidney function was defined as an eGFR below age-appropriate reference values.

Risk factor analysis

Potential risk factors for kidney impairment included metabolic abnormalities, family history, genetic mutations, ultrasound findings, and demographic characteristics (age and sex). The cumulative effect of multiple risk factors was also evaluated.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 27.0 and MedCalc version 23.4.5. Categorical variables were analyzed using chi-square or Fisher's exact tests, whereas continuous variables were compared using parametric or nonparametric tests as appropriate. Multivariate analysis was performed using binary logistic regression to identify independent predictors of renal impairment. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Receiver operating characteristic (ROC) curve analysis was used to determine optimal cutoff values and to assess the predictive performance of the model. A p value <0.05 was considered to indicate statistical significance.

Ethical considerations

This study was conducted in accordance with the Declaration of Helsinki and was approved by the local Ethics Committee. Ethics approval is not required at our institution to publish anonymous data. Written informed consent was obtained from the parents of each patient for every admission to the Department of Pediatric Nephrology and Dialysis at the Specialized Hospital for Active Treatment of Children's Diseases "Prof. Ivan Mitev"; patient consent forms were retained in medical files.

Results

Study population characteristics

This was an ambispective clinical–epidemiological study that included 176 pediatric patients from all regions of the country. All the children were hospitalized at the Department of Pediatric Nephrology and Dialysis, Specialized Hospital for Active Treatment of Children's Diseases "Prof. Ivan Mitev", between January 2020 and December 2024. The sex distribution for the study population was nearly equal, i.e., 89 boys (50.6%) and 87 girls (49.4%). Regarding the age distribution at disease presentation, 41 patients (23.3%) were aged 0–1 year, 39 (22.2%) were aged 1–3 years, 40 (22.7%) were aged 3–7 years, 46 (26.1%) were aged 7–14 years, and 10 (5.7%) were aged 14–18 years. The largest proportion of patients belonged to the 7–14-year age group. With respect to the ultrasound findings, microlithiasis was the most frequent diagnosis, observed in 79 patients (44.9%), followed by nephrolithiasis, observed in 70 patients (39.8%), and nephrocalcinosis, observed in 27 patients (15.3%).

Metabolic factors

Metabolic abnormalities were highly prevalent among the study population and were identified in most patients (75%). Overall, approximately three-quarters of the children were found to have at least one metabolic risk factor contributing to lithogenesis. Among the evaluated metabolic parameters, hypocitraturia was the most frequently observed abnormality, detected in 75.7% of the patients for whom data were available, followed

by hyperuricosuria in 53.5%. Hypercalciuria was also common, present in 43.2% of the cohort, whereas hyperoxaluria was the least frequent metabolic disorder, identified in 33.8% of patients. For a significant proportion of children, multiple metabolic abnormalities coexisted. Differences were more pronounced by age. Hypercalciuria and hyperuricosuria were significantly more common in younger children, particularly in infants (38.2% and 28.3%, respectively), with their prevalence decreasing with increasing age. Similarly, hypocitraturia was more frequently observed in younger age groups (34,8%), while normal citrate levels were more likely in older children.

Family history and genetic factors

A positive family history was present in 61.9% of the patients. A first-degree positive family history (parents or siblings) was identified in 56 children (31.8%), a second-degree positive family history (grandparents, aunts, or uncles) was identified in 23 children (13.1%), and a family history in both lineages was identified in 30 patients (17.0%).

Genetic mutations were identified in 16.5% of the patients (Figure 1). Among the 29 detected mutations, the most frequent was CLDN16 (familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC)), which accounted for 24.1% of the cases, followed by CYP24A1 (idiopathic infantile hypercalcemia, type 1 (HCINF1)), which accounted for 17.2% of the cases. Several mutations were observed only in isolated cases, for example, CLCNKB (Bartter syndrome type III), HOGA1 (primary hyperoxaluria type III (PH3), and HPRT1 (Lesch-Nyhan syndrome), with each accounting for 3.4% of the cases. An age distribution analysis revealed that genetic

mutations were predominantly identified in younger children, with the majority of cases occurring in infants aged 0–1 years (69.0%).

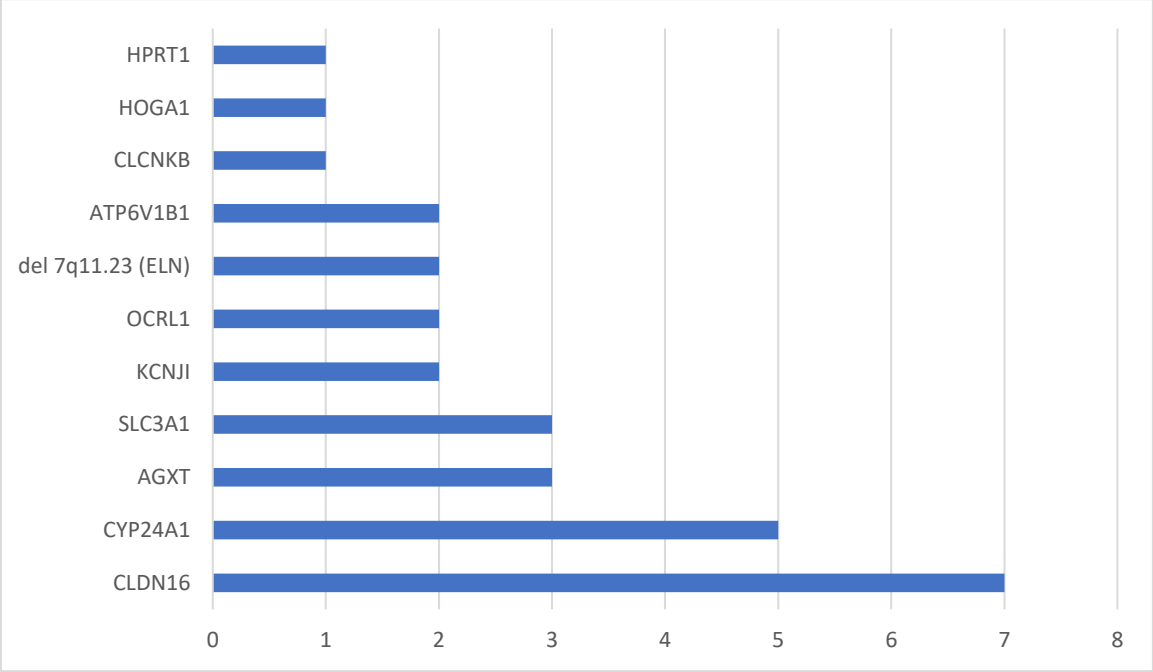


Fig. 1 Number of children with genetic mutations

Kidney failure

Kidney function was categorized according to the KDIGO classification. The mean estimated glomerular filtration rate (eGFR) in the study population was 150.65 ± 40.72 mL/min/1.73 m², with a wide range from 8 to 240 mL/min/1.73 m². Most patients (148; 84.1%) exhibited hyperfiltration (≥120 mL/min/1.73 m²), followed by normal renal function (G1) (8.5% of patients). In contrast, reduced kidney function was relatively uncommon, with only a small proportion of patients classified within CKD stages G2–G5. Severe kidney impairment (G5) was observed in only one patient (0.6%).

Ultrasound findings and risk of kidney injury

The association between ultrasound findings and kidney injury was evaluated by comparing imaging characteristics in patients with a reduced eGFR. The analyzed parameters included stone size (<5 mm, 5–10 mm, and >10 mm), type of ultrasound diagnosis (nephrolithiasis, microlithiasis, and nephrocalcinosis), increased renal parenchymal echogenicity, and hydronephrosis. Statistical analysis revealed a significant association with reduced kidney function for only the type of ultrasound finding ($p=0.004$). Specifically, compared with nephrolithiasis (12.5%) and microlithiasis (25%), nephrocalcinosis was associated with a significantly greater proportion of patients with a decreased eGFR (62.5%). In contrast, no statistically significant associations were found between reduced eGFR and stone size, increased parenchymal echogenicity, or the presence of hydronephrosis.

Metabolic factors and risk of kidney injury

The associations between metabolic abnormalities and kidney injury were evaluated by comparing their distributions in patients with a reduced eGFR. Statistical analysis revealed significant associations between decreased kidney function and two metabolic factors: hypercalciuria (87.5%; $p=0.022$) and hyperoxaluria (100%; $p=0.035$). There was significantly higher prevalence of these abnormalities among patients with a reduced eGFR. No statistically significant associations were detected between renal impairment and hyperuricosuria or hypocitraturia.

Family history, genetic factors and risk of kidney injury

The relationships among familial predisposition, genetic mutations, and kidney injury were evaluated in the study cohort. Statistical analysis revealed a significant association between a reduced eGFR and the presence of a confirmed genetic mutation (87.5%; $p<0.001$). The prevalence of kidney failure was significantly higher among patients with identified genetic mutations than among those without such mutations. In contrast, no statistically significant association was observed between kidney damage and family history alone.

Predictive model for kidney injury

Based on the initial analyses, several factors, including confirmed genetic mutations, hypercalciuria, hyperoxaluria, and nephrocalcinosis, were significantly associated with kidney impairment. Given that decreased kidney function was defined as a dichotomous outcome, a multivariate binary logistic regression model was applied to identify independent predictors. In addition to the aforementioned variables, potential confounders such as age and sex were also included in the analysis. Hyperoxaluria was excluded from the regression model because of the absence of patients without this factor among those with kidney damage, as well as the limited number of patients with a reduced eGFR (n=8), which restricted the statistical power.

Univariate analysis revealed significant associations of kidney injury with genetic mutation, age, nephrocalcinosis, and hypercalciuria (Table 1).

- The strongest predictor was the presence of a *genetic mutation*, which was associated with an approximately 46-fold increased risk of kidney

impairment among patients with mutations compared with patients without mutations.

- *Nephrocalcinosis* was the second strongest predictor, associated with an approximately 11-fold increased risk, followed by *hypercalciuria*, which conferred an approximately 10-fold increased risk.
- *Age* demonstrated a protective effect, with each additional year associated with an approximately 52% reduction in risk.

Table 1. Odds ratios and 95% confidence intervals for the studied variables associated with kidney impairment

Parameter	Comparison	Univariate				Multivariate			
		OR	95% CI		p	OR	95% CI		p
			Lower	Upper			Lower	Upper	
Confirmed genetic mutation	Yes/No	46,455	5,451	395,905	**<0,001**	18,469	1,939	175,881	**0,011**
Age	Increase by 1 year	0,484	0,254	0,920	**0,027**	0,675	0,374	1,217	0,191
Nephrocalcinosis	Yes/No	11,061	2,468	49,565	**0,002**				
Hypercalciuria	Yes/No	10,043	1,208	83,483	**0,033**				
Sex	Female/Male	1,748	0,405	7,549	0,454				

To account for the combined effect of these variables and adjust for confounding, a multivariate logistic regression model was constructed using a backward conditional approach. In the final model, only two variables remained: confirmed genetic mutation

and age. Both variables retained the same direction of effect; however, statistical significance was maintained only for genetic mutations. In the adjusted model, the presence of a genetic mutation was associated with an approximately 18.5-fold increased risk of kidney dysfunction, while the protective effect of age was attenuated, with an estimated 32% reduction in risk per additional year.

Predictive equation for kidney impairment

On the basis of the multivariate logistic regression analysis, a predictive model for kidney impairment was developed using the following equation: $P = \frac{1}{1 + e^{-z}}$ where $Z = 2.916 \times (\text{genetic mutation}) - 0.393 \times (\text{age}) - 3.569$

The coefficients included in the model were derived from the regression analysis presented in Table 2. In this equation, the variable *genetic mutation* is binary, taking a value of 1 for the presence of a confirmed mutation and 0 for the absence of a mutation, and *age* is included as a continuous variable.

Table 2. Multiple binary logistic regression analysis results

Parameter							**95% C.I. for EXP(B)**	
	B	S.E.	Wald	df	Sig.	Exp(B)	Lower	Upper
Confirmed genetic mutation	2,916	1,150	6,431	1	0,011	18,469	1,939	175,881
Age	-0,393	0,301	1,711	1	0,191	0,675	0,374	1,217
Constant	-3,569	1,183	9,101	1	0,003	0,028		

Model performance and validation

The predictive performance of the developed logistic regression model was evaluated using receiver operating characteristic (ROC) curve analysis based on the calculated

probabilities for each patient. An optimal cutoff value for discriminating between patients with and without kidney impairment was determined using the Youden index (maximum sensitivity + specificity − 1). The analysis revealed a statistically significant threshold probability of ≥ 0.124. The area under the ROC curve (AUC) was 0.872 ($p < 0.001$), indicating very good discriminative ability (Fig. 2).

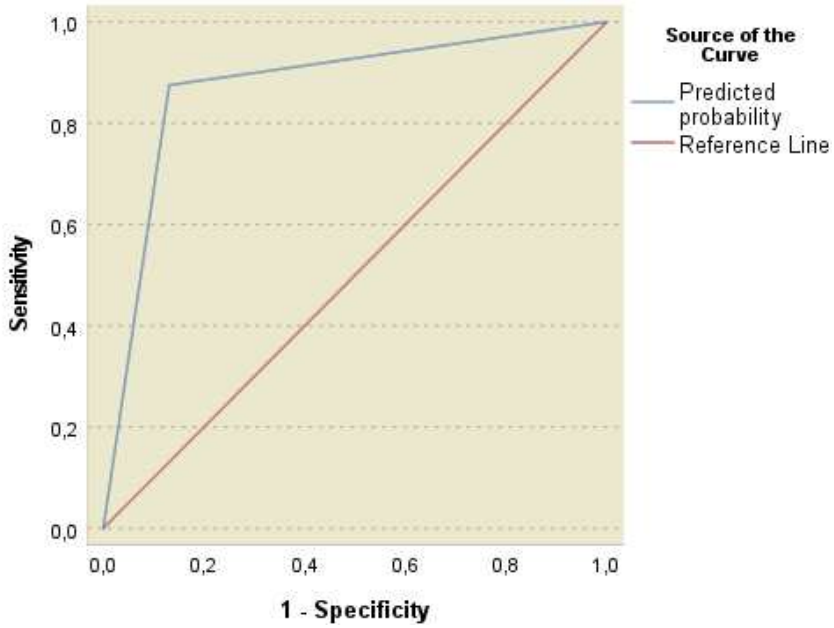


Fig. 2 Receiver operating characteristic (ROC) curve for the predicted probability derived from the binary logistic regression model for discriminating between patients with and without kidney impairment (area under the curve [AUC] = 0.872; $p < 0.001$)

At this cutoff, the model demonstrated high diagnostic performance, with a sensitivity of 88% and a specificity of 87%. The model also showed high overall accuracy (87%) and excellent negative predictive value (99%), although the positive predictive value was relatively low (24%) (Table 3).

Table 3. Cutoff value for the predicted probability derived from the binary logistic regression model for discriminating between patients with and without kidney impairment, along with validation metrics

Parameter	Cutoff value	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Accuracy (%)
Predicted probability	≥ 0,124	88	87	24	99	87

Risk stratification

Using the identified predictors, a risk stratification model for kidney damage was developed. The following variables were considered: confirmed genetic mutation, age, nephrocalcinosis, and hypercalciuria. Although hyperoxaluria was also associated with increased risk, it was excluded because of a high proportion of patients with missing data (61.4%), which could lead to significant bias in the analysis. To facilitate clinical applicability, an age cutoff value was determined using ROC analysis. A threshold of ≤3.5 years was identified as optimal (AUC 0.843; $p < 0.001$), demonstrating excellent sensitivity (100%) and negative predictive value (100%) but lower specificity (57%) (Fig. 3 and Table 4).

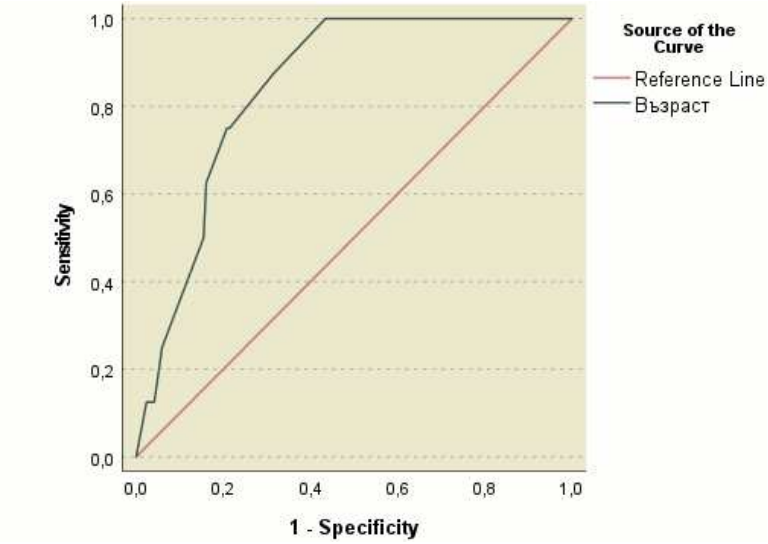


Fig. 3 Receiver operating characteristic (ROC) curve for age for determining the optimal cutoff value for discriminating between patients with and without kidney impairment (area under the curve [AUC] = 0.843; $p < 0.001$)

Table 4. Age cutoff for kidney impairment discrimination and validation

Parameter	Cutoff value	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Accuracy (%)
Age (years)	≤ 3,5	100	57	10	100	59

On the basis of these findings, patients were stratified into three risk categories (Table 5):

- High risk: presence of at least two of the following factors: confirmed genetic mutation, age ≤3.5 years, nephrocalcinosis, and hypercalciuria
- Intermediate risk: presence of only one of the above risk factors
- Low risk: absence of all four risk factors

Table 5. Risk stratification criteria for kidney impairment

Risk of kidney impairment		
Low	Intermediate	High

Absence of all four risk factors	One risk factor present (genetic mutation, age ≤3.5 years, nephrocalcinosis, or hypercalciuria)	≥2 risk factors present (genetic mutation, age ≤3.5 years, nephrocalcinosis, or hypercalciuria)

Discussion

The present study provides a comprehensive evaluation of disease severity in pediatric nephrolithiasis, microlithiasis, and nephrocalcinosis, integrating clinical, diagnostic and laboratory findings and kidney-function data. The results highlight the multifactorial nature of renal impairment risk in this population. Among metabolic abnormalities, *hypocitraturia* was the most frequently identified (75.7%), followed by *hyperuricosuria* (53.5%) and *hyperoxaluria* (33.8%). The high prevalence of hypocitraturia is consistent with the findings of previous reports indicating that it is the second most common metabolic abnormality, with a prevalence of up to 40–60%. However, in the present study, an even higher proportion was observed. These findings underscore the key role of citrate as an inhibitor of crystallization and suggest that citrate deficiency represents one of the principal mechanisms of lithogenesis in the studied population. Age-stratified analysis revealed significant differences. *Hypercalciuria and hyperuricosuria* were markedly more prevalent in infancy, which may be explained by the immaturity of renal tubular function and the influence of dietary factors during this period. *Hypocitraturia* was more characteristic of early childhood (2–3 years), and its prevalence decreased with increasing age. These findings are consistent with results reported in the literature, emphasizing the age-dependent nature of metabolic abnormalities and their relationship to the physiological maturation of renal function. Of particular importance is the observed *coexistence of multiple metabolic abnormalities* in a substantial proportion of

patients (40.3%). This finding supports the concept that lithogenesis is rarely the result of a single factor but is more commonly driven by a combination of metabolic disturbances. Overall, our results align with the current understanding of nephrolithiasis pathogenesis, highlighting the role of an imbalance between promoters and inhibitors of crystallization.

A high prevalence of *positive family history* was observed among the studied cohort (61.9%), most commonly involving first-degree relatives. This percentage exceeds that reported in the literature, where approximately 40% of children with nephrolithiasis are described as having a familial predisposition. Genetic analysis revealed that 16.5% of the children had a confirmed mutation, a finding that is consistent with previously reported data (10–20%). Notably, patients with confirmed mutations were predominantly in early childhood, supporting the role of genetic factors in early disease onset. The most frequently identified mutations *(CLDN16* and *CYP24A1)* are associated with disturbances in calcium metabolism, which may explain the observed statistically significant association between genetic mutations and *hypercalciuria* and *hyperoxaluria*. The absence of a significant association between genetic mutations and other metabolic abnormalities suggests that some of these factors may be strongly influenced by external determinants, such as diet and lifestyle. Our findings highlight the need for a comprehensive approach in patient evaluation, incorporating both genetic and metabolic investigations. The high prevalence of a positive family history and the substantial proportion of genetic mutations underscore the important role of hereditary factors, particularly in early-onset disease. Moreover, the observed significant association between genetic mutations and specific metabolic

abnormalities, such as *hypercalciuria* and *hyperoxaluria*, supports the hypothesis that a distinct subgroup of patients has *monogenic forms of the disease*. This subgroup is characterized by earlier disease onset and a potentially more severe clinical course, necessitating a more aggressive diagnostic and therapeutic approach.

Renal-function analysis revealed that most patients had a normal or elevated eGFR, with hyperfiltration observed in 84.1% of patients. This finding is particularly relevant, as hyperfiltration has been proposed as an early marker of renal injury and a potential predictor of progression to chronic kidney disease (CKD). Among the identified risk factors for renal impairment, nephrocalcinosis showed the strongest association with a reduced eGFR, in agreement with the findings of previous studies that demonstrated a link between a reduced eGFR and progressive renal damage. The high prevalence of *glomerular hyperfiltration* observed in most patients may reflect an early adaptive response of the kidney to underlying metabolic and structural alterations. In pediatric patients with nephrolithiasis and nephrocalcinosis, hyperfiltration is thought to result from increased single-nephron filtration and compensatory hemodynamic changes, particularly in the presence of tubular dysfunction or subclinical injury. Several mechanisms may contribute to this phenomenon. First, metabolic disturbances, such as hypercalciuria and hyperoxaluria, can induce tubular stress and alter intrarenal hemodynamics, leading to increased glomerular filtration. Second, in conditions associated with nephrocalcinosis, calcium deposition within the tubules may impair tubular reabsorption and trigger compensatory hyperfiltration at the glomerular level. Third, hyperfiltration may represent an early stage of kidney involvement preceding a measurable decline in renal function, especially in children with preserved nephron

mass. Importantly, although hyperfiltration may initially maintain or even increase the eGFR, it is increasingly recognized as a *potential early marker of kidney injury*. Persistent hyperfiltration can lead to glomerular hypertension, progressive nephron damage, and an eventual decline in kidney function. This may explain why, despite a predominance of normal or elevated eGFR values in the present cohort, a subset of patients—particularly those with nephrocalcinosis and underlying metabolic or genetic disorders—exhibited reduced kidney function. These findings suggest that hyperfiltration should not be interpreted as a benign phenomenon but rather as a compensatory and potentially maladaptive response, highlighting the need for the early identification and close long-term follow-up of at-risk patients.

The lack of a significant association between reduced kidney function and most ultrasound parameters, such as stone size, hydronephrosis, and increased parenchymal echogenicity, suggests that these findings may reflect transient or reversible conditions rather than sustained structural damage. In nephrolithiasis, even larger calculi do not necessarily lead to permanent kidney impairment unless they are associated with prolonged obstruction or recurrent episodes. Similarly, hydronephrosis represents a functional consequence of obstruction, which, if promptly relieved, may not result in the long-term deterioration of kidney function. Increased parenchymal echogenicity, although considered a marker of underlying kidney pathology, is a nonspecific finding and may not reliably indicate the severity or chronicity of kidney damage, particularly in early or mild disease stages.

In contrast, nephrocalcinosis involves the diffuse intrarenal deposition of calcium salts within the tubular and interstitial compartments and is more directly associated

with chronic tubular injury, inflammation, and interstitial fibrosis. This structural involvement provides a pathophysiological basis for the observed association with reduced eGFR. Furthermore, compared with isolated stone disease, nephrocalcinosis is frequently linked to underlying metabolic and genetic disorders, which tend to have a more persistent and progressive course. These factors likely explain why nephrocalcinosis, rather than other ultrasound findings, emerged as a significant predictor of kidney injury in the present cohort.

Among metabolic factors, hypercalciuria and hyperoxaluria were significantly associated with decreased kidney function, highlighting their role not only in lithogenesis but also in the progression of kidney injury. A key finding of this study is the strong association between genetic mutations and kidney impairment. Patients with confirmed genetic abnormalities demonstrated a markedly increased risk of a reduced eGFR, supporting the concept that genetic forms of nephrolithiasis and nephrocalcinosis are associated with more severe disease and a poorer prognosis. The cumulative effect of risk factors was clearly related to kidney impairment, with a significantly greater risk observed in patients with two or more coexisting factors. These findings support the multifactorial nature of disease progression and emphasize the importance of a comprehensive risk assessment. A major strength of this study is the development of a predictive model for kidney impairment using multivariate logistic regression. Through this model, confirmed genetic mutation was identified as the strongest independent predictor, followed by age. The model had high sensitivity and specificity, suggesting that it has potential clinical utility for the early identification of high-risk patients.

Despite the strengths of this study, several limitations should be considered. First, the high prevalence of hyperfiltration raises the question of whether hyperfiltration represents a compensatory mechanism or an early stage of renal injury. The lack of long-term follow-up limited the ability to determine its prognostic significance. Second, the relatively small number of patients with genetic mutations limited the ability to assess the impact of specific genotypes on renal outcomes. Finally, although the predictive model demonstrated strong diagnostic performance, external validation in larger and independent cohorts is needed.

Conclusions

Kidney impairment in children with nephrolithiasis and nephrocalcinosis is driven primarily by underlying metabolic and genetic factors rather than by the presence of stones alone. Nephrocalcinosis, hypercalciuria, and hyperoxaluria were significantly associated with decreased renal function, and confirmed genetic mutations emerged as the strongest independent predictor of kidney injury. Younger age was identified as an additional risk factor, highlighting the vulnerability of early childhood. The proposed predictive model demonstrated good diagnostic performance and may serve as a useful clinical tool for the early identification of high-risk patients. Furthermore, the cumulative burden of risk factors was strongly associated with an increased risk of impaired kidney function, supporting the need for comprehensive evaluation in all affected children. Early diagnosis, targeted metabolic and genetic assessments, and individualized management strategies are essential for preventing long-term kidney damage and improving outcomes in this population.

Declarations

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Competing interests

The authors declare that there are no conflicts of interest regarding the publication of this article.

Author contributions

Greta Mihneva-Kirilova designed the study, analyzed the data and wrote the manuscript. The other authors contributed as co-authors of this manuscript and participated in the investigations listed in the article.

Data, material and/or code availability

The data generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics approval

This study was conducted in accordance with the Declaration of Helsinki and was approved by the local Ethics Committee. Ethics approval is not required at our institution to publish anonymous data.

Consent to participate

Written informed consent was obtained from the parents of each patient for every admission to the Department of Pediatric Nephrology and Dialysis at the Specialized Hospital for Active Treatment of Children's Diseases "Prof. Ivan Mitev"; patient consent forms were retained in medical files. For patients who underwent genetic testing, additional informed consent was obtained from parents or legal guardians prior to analysis.

Consent for publish

Not applicable.

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