Original Article
Trends of renal biopsy in pediatric patients at Tanta University Hospital, Egypt.

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ABSTRACT

Introduction: Renal biopsy is crucial in pediatric nephrology for accurate diagnosis and management.
Aim of the study: This study aimed to investigate the indications, complications, and results of renal biopsies in pediatric patients at Tanta University Hospital over 10 years.
Methods: A retrospective analysis was conducted on 515 pediatric patients who underwent renal biopsy from 2013 to 2022. Data on demographics, indications, biopsy methods, complications, and histopathological findings were collected from medical records.
Results: The mean age was 8.2 years, with a slight female predominance (52.53%). Nephrotic syndrome was the leading indication (46.99%), followed by systemic lupus erythematosus (SLE) (24.66%). In nephrotic syndrome cases, minimal change disease was the most prevalent (23.69%). Lupus nephritis class III was predominant in SLE patients (11.07%). Electron microscopy (EM) revealed findings of Alport syndrome in 13 cases of nephrotic syndrome with extrarenal manifestations, despite normal light microscopy findings in 10 cases. In recurrent gross hematuria, IgA nephropathy was the leading cause (5.38%) identified by immunofluorescence (IF).
Conclusion: Renal biopsy plays a crucial role in pediatric nephrology, with nephrotic syndrome and SLE being the most common indications. Minimal change disease (MCD) predominated in nephrotic syndrome cases, while class III was most prevalent in lupus nephritis. EM and IF proved invaluable in diagnosing conditions like Alport syndrome and IgA nephropathy, even when light microscopy (LM) appeared normal.
Keywords: Renal biopsy, pediatric nephrology, nephrotic syndrome, lupus nephritis, electron microscopy

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INTRODUCTION

Renal biopsy is a well-established diagnostic tool in pediatric nephrology, widely used to facilitate accurate diagnosis and guide the management of various kidney disorders [1, 2]. Nephrotic syndrome is the most common indication for renal biopsy in pediatric patients, accounting for 29% to 37% of cases [3]. Other frequent indications include unexplained renal failure, isolated non-nephrotic proteinuria, glomerular hematuria, and renal transplant dysfunction [4].

This procedure provides precise diagnoses, particularly for glomerular disorders, while also offering valuable prognostic information and guiding treatment decisions [2, 4]. The advantage of automated biopsy devices and ultrasound-guided kidney localization has significantly enhanced the efficacy and safety of percutaneous renal biopsies, reducing the incidence of serious complications to less than 1% [4]. The incidence of severe complications is low, with rates around 0.05% to 0.06% [5, 6].

Open biopsy is indicated in situations where percutaneous methods are contraindicated, such as in patients with bleeding disorders or solitary kidneys [7]. The choice of sedation technique has been a subject of recent investigation, with intravenous sedation showing comparable risk to general anesthesia [5].While many renal pathologies observed in adults can also affect children, the relative frequencies of specific conditions may differ substantially in pediatric populations [8]. Epidemiological analyses of various registries have revealed that the spectrum of renal diseases in children varies across geographic locations [9]. This variability underscores the importance of region-specific studies to elucidate the prevalence and characteristics of pediatric renal disorders.

Numerous investigations have reported on the distribution of diagnostic categories in large series of pediatric renal biopsies [10]. Although direct comparisons between studies may be challenging due to variations in biopsy protocols and indications across centers and countries, these reports provide valuable insights into the most commonly encountered renal entities in children [11].

Given the importance of region-specific data, this retrospective study aimed to investigate the indications, complications, and results of renal biopsies performed in pediatric patients at Tanta University Hospital, Egypt over 10 years.

METHODS

This retrospective study was conducted at the Nephrology Unit of the Pediatric Department, Our University Hospital, Egypt, to describe the results of biopsies from native kidneys performed over ten years (between January 2013 and December 2022) by using the real-time US guidance.

Data collection: Patient information was extracted from medical records, including demographic data (age and sex), indications for renal biopsy, biopsy methods employed, complications arising from the procedure, and adequacy of obtained samples. Results from LM were analyzed, along with electron microscopy (EM) and immunofluorescence (IF) findings when indicated.

The study was conducted in accordance with the Declaration of Helsinki and adhered to the principles of

good clinical practice. Approval was obtained from the Ethics Committee of the Faculty of Medicine, Our University. As this was a retrospective analysis of existing medical records, no additional risks to patients were identified.

Exclusion criteria: Biopsy samples containing fewer than eight glomeruli were excluded to ensure diagnostic adequacy and consistency with established histopathological evaluation standards. The biopsy cores should include glomeruli, arteries/arterioles, tubules, and interstitium.

Biopsy procedure: Written consent was taken from parents or caregivers of all patients before the procedure. A coagulation profile, including prothrombin time, activated partial thromboplastin time, and platelet count, was performed as routine work before the procedure. Patients with an international normalized ratio of >1.5 or a platelet count <100,000 were not biopsied. The patients were positioned in a prone position with a pillow under the abdomen to support the loin. The kidneys were scanned to determine the optimal biopsy site. A US machine (Siemens Sono-Line G60F, Germany) with a convex array transducer 3.5 MHz was used. All patients received local anesthesia and sedation before the procedure. A semi-automated gun performed a biopsy with an 18-gauge needle. The gun needle was inserted under US guidance into the abdominal wall through a small skin incision. The needle was then advanced until the tip was seen within the outer cortex. The gun was fired to take the core specimen. The number of insertions was determined based on gross visual inspection of each core for adequacy, considering typical features suggestive of renal cortex. Since a renal pathologist was not available on-site, immediate microscopic evaluation for glomerular content could not be performed. However, at least two visually adequate cores were obtained and submitted for formal histopathological examination. LM examination was done in all cases. The sample was fixed in 10% formaldehyde solution, and sections were stained with hematoxylin and eosin, periodic acid Schiff, and Jones' methenamine silver stain. The samples for the IF study were submitted in saline as transport medium, and IF staining using polyclonal antisera against human IgG, IgM, IgA, and C1q was performed. The samples for EM examination were fixed in glutaraldehyde media immediately after obtaining the tissue and sent for examination.

Post-procedure follow-up: All patients were kept on strict bed rest for 6 hours post-procedure. A post-procedure US scan was performed 6 h after the procedure and repeated after 24 h of biopsy. Post-procedure complications that required surgical intervention or blood transfusion were considered. The patients were followed up by urine examination for two weeks post-biopsy.

Nephrotic syndrome (NS), steroid-dependent NS (SDNS), and steroid-resistant NS (SRNS) were defined as per the standard Kidney Disease Improving Global Outcomes (KDIGO) in Children definitions [12]. Juvenile systemic lupus erythematosus (SLE) was diagnosed according to the revised American College of Rheumatology criteria for diagnosis of SLE [13]. Figure 1

STATISTICAL ANALYSIS

Statistical analysis was done by SPSS v26 (IBM Inc., Chicago, IL, USA).

Quantitative variables were presented as mean and standard deviation (SD) and compared between the measurements utilizing an unpaired Student's t-test. Qualitative variables were presented as frequency (%).

RESULTS

This distinction arises because the study initially included 527 biopsies but excluded 12 due to inadequacy (leaving 515 biopsies). These 515 biopsies were performed on 491 unique patients, with 24 patients requiring follow-up biopsies.Twenty-four patients underwent follow-up renal biopsy. Two cores from each patient were sent for histopathological examination; there was a mean of 12 glomeruli present in each specimen. All specimens were examined with LM (100%), and 30 (5.8%) cases were examined by IF, while only 20 samples were examined with EM (3.88%).

The demographic data of the patients studied encompassed 491 patients, with a mean age of 8.2 years (SD ± 4.34 years). Sex distribution analysis showed a slight predominance of female patients, accounting for 52% (n = 256) of the cohort, compared to 235% (n = 48) male patients. **Table 1**

Nephrotic syndrome emerged as the predominant indication in our center, accounting for 46.99% (n = 242) of all biopsies. Within this category, steroid-dependent cases were most frequent (23.5%, n = 121), followed by atypical presentations (12.23%, n = 63), and steroid-resistant cases (6.02%, n = 31). SLE represented the second most common indication, comprising 24.66% (n = 127) of biopsies, either for diagnosis of lupus nephritis in 22.33% (n = 115) or for follow-up biopsy in 2.33% (n =12). Other significant indications included hemolytic uremic syndrome (HUS) with atypical or prolonged course (6.21%, n = 32), recurrent gross hematuria (6.8%, n = 35), and unexplained acute renal failure (ARF) (6.6%, n = 34). **Table 2**

In cases of nephrotic syndrome (46.99%, n = 242), MCD was the predominant finding (23.69%, n = 122), followed by FSGS (19.13%, n = 47) and mesangioproliferative glomerulonephritis (6.8%, n = 35). Among SLE patients (24.66%, n = 127), lupus nephritis class III was most prevalent (11.07%, n = 57), followed by class IV (6.21%, n = 32) and class II (4.27%, n = 22). In cases of recurrent gross hematuria (6.8%, n = 35), mesangioproliferative changes were observed in 5.83% (n = 30) of biopsies. For unexplained chronic renal failure (CRF) (4.47%, n = 23), diffuse sclerosis with tubular atrophy was the most common finding (1.75%, n = 9), while in cases of unexplained ARF (6.6%, n = 34), crescentic glomerulonephritis was the predominant pathology (3.5%, n = 18). **Table 3**

Notably, in 14 cases (2.72%) of nephrotic syndrome with extrarenal manifestations, EM revealed Alport syndrome in all instances, despite 10 cases (1.94%) appearing normal under LM. This underscores the critical role of EM in diagnosing certain genetic renal disorders that may not be apparent through conventional LM. While one case with abnormal LM (membranoproliferative) revealed subendothelial deposits, Mesangial proliferation and deposits, effaced podocytes with sheded pedicles by EM, this case was diagnosed by genetic and immunological studies as autoimmune lymphoproliferative syndrome (ALPS)

and DiGeorge. Additionally, in one case (0.19%) of unexplained CRF with extrarenal manifestations, EM revealed thin, fragmented glomerular basement membranes (GBM) with variable diameters and totally atrophied glomerular and tubular cells. This finding provided crucial insights into the underlying pathology, which was initially diagnosed as end-stage renal disease (ESRD) based on LM findings of diffuse sclerosis with tubular atrophy. **Table 4**

In cases of recurrent gross hematuria, which accounted for 30 cases (5.83%) of the IF examinations. Interestingly, all these cases appeared normal under LM, emphasizing the limitations of LM in diagnosing certain renal pathologies. The IF analysis revealed that IgA nephropathy was the predominant underlying cause, identified in 3.69% (n = 19) of these cases. This was followed by mesangioproliferative IgG/IgM deposits, observed in 1.75% (n = 9) of cases. A small proportion (0.39%, n = 2) showed evidence of IgA vasculitis. These findings underscore the crucial role of IF in elucidating the etiology of recurrent gross hematuria, particularly in cases where LM showed nonspecific abnormalities. **Table 5**

The most common complication reported post-biopsy was pain at the site of biopsy that was treated with analgesia (77.5 %). Transient gross hematuria without urine retention was reported in 50 patients (9.7%) after biopsy. A small perinephric hematoma was noted in 13 patients (2.52%) that resolved spontaneously. No major complications that require surgical intervention occurred.

Table 1: Demographic data of the patients studied

		(n=491)
Age (years)		8.2 ± 4.34
Sex	**Male**	235 (48%)
	Female	256 (52%)

Data are presented as mean ± SD or frequency (%).

Table 2: Indications of renal biopsy of the studied patients

Total	**515 (100%)**
Nephrotic syndrome	242 (46.99%)
Steroid dependent	121 (23.5%)
Atypical presentations	63 (12.23%)
Steroid resistant	31 (6.02%)
Infantile nephrotic syndrome	14 (2.72%)
Follow-up biopsy	12 (2.33%)
Systemic lupus erythematosus	127 (24.66%)
Lupus nephritis	115 (22.33%)
Follow-up biopsy	12 (2.33%)
Hemolytic uremic syndrome with atypical or prolonged course	32 (6.21%)
Recurrent gross hematuria	35 (6.8%)
Unexplained chronic renal failure	23 (4.47%)
Unexplained acute renal failure	34 (6.6%)
Acute glomerulonephritis	22 (4.27%)

Data are presented as frequency (%).

Table 3: Light microscopy findings of renal biopsy of the studied patients

Total	**515 (100%)**
Nephrotic syndrome	242 (46.99%)
Minimal change disease	122 (23.69%)
Focal and segmental glomerulosclerosis	47 (9.13%)
Mesangioproliferative glomerulonephritis	35 (6.8%)
Diffuse mesangial sclerosis	7 (1.36%)
Cyclosporine toxicity	13 (2.52%)
Membranoproliferative glomerulonephritis	12 (2.33%)
Membranous	3 (0.58%)
Amyloidosis	3 (0.58%)
Systemic lupus erythematosus	127 (24.66%)
Lupus nephritis class I	14 (2.72%)
Lupus nephritis class II	22 (4.27%)
Lupus nephritis class III	57 (11.07%)
Lupus nephritis class IV	32 (6.21%)
Lupus nephritis class V	2 (0.39%)
Recurrent gross hematuria	35 (6.8%)
Mesangioproliferaive	30 (5.83%)
Normal	5 (0.97%)
Unexplained chronic renal failure	23 (4.47%)
Chronic interstitial nephritis	4 (0.78%)
Diffuse sclerosis with tubular atrophy	9 (1.75%)
Nephronophithesis	6 (1.17%)
Tubular necrosis suggestive of pyelonephritis	2 (0.39%)
Amyloidosis	2 (0.39%)
Hemolytic uremic syndrome Thrombotic microangiopathy	32 (6.21%)
Unexplained acute renal failure	34 (6.6%)
Acute tubular necrosis	12 (2.33%)
Crescentic glomerulonephritis	18 (3.5%)
Acute cortical necrosis	2 (0.39%)
Anti- Glomerular basement membrane disease	1 (0.19%)
Vasculitis	1 (0.19%)
Glomerulonephritis	22 (4.27%)
Crescentic glomerulonephritis	17 (3.3%)
Mesangioproliferative glomerulonephritis	5 (0.97%)

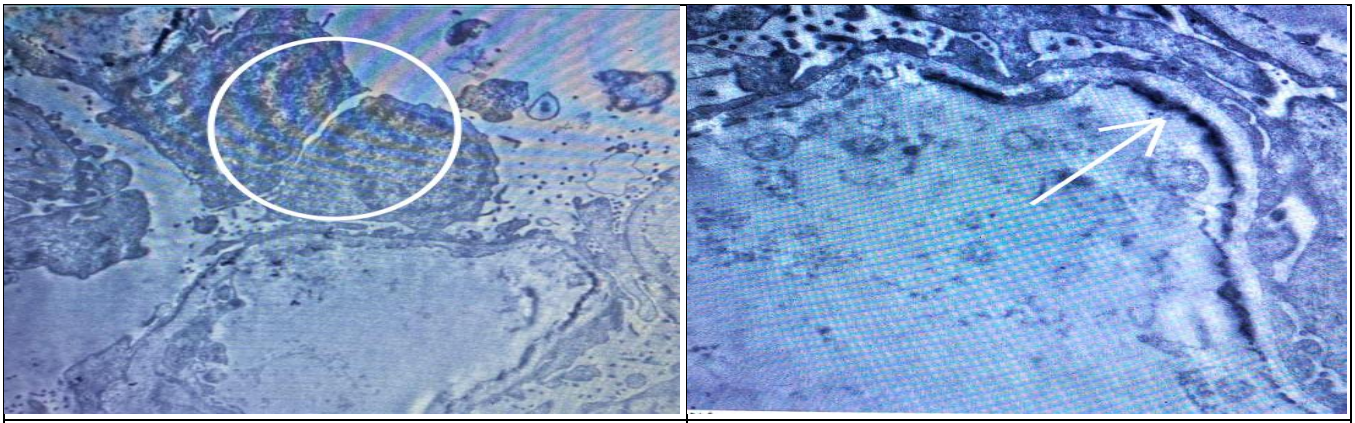
Data are presented as frequency (%).

Table 4: Electron microscopic findings of the studied patients

Indication	**Number (%)**	**Light microscope result**	**Electron microscope result**	**Number (%)**
Nephrotic syndrome with extrarenal manifestation	14 (2.72%)	Normal 10 (1.94%) FSGS 3 (0.58%)	1- Irregular thickening of the glomerular basement membrane with splitting and fragmentation of lamina densa **(Alport syndrome)**	13 (2.52%)
		Membranoproliferative	2-Subendothelial deposits, Mesangial proliferation and deposits, effaced podocytes with shed pedicles (ALPS syndrome and digeorge)	1 (0.19%)
Recurrent gross hematuria	5 (0.97%)	Normal	Thin basement membrane Alport findings	3 (0.58%) 2 (0.39%)
Unexplained chronic renal failure with extrarenal manifestation	1 (0.19%)	Diffuse sclerosis with tubular atrophy (End-stage renal disease)	Thin, fragmented GBM with variable diameters totally atrophied glomerular and tubular cells	1 (0.19%)

Table 5: Recurrent gross hematuria immunofluorescence results of the studied patients

Indication	N (%)	Light microscope result	Immunofluorescence result (IF)	N (%)
Recurrent gross hematuria	30 (5.83%)	Mesangioproliferative	IgA Neph Vasculitis IgA Mesangioproliferative IgG/IgM	19 (3.69%) 2 (0.39%) 9 (1.75%)



(A) **(B)**

Figure 1: EM (A) Subendothelial deposits and effacement of basement membrane (B) Mesangial proliferation and deposits.

DISCUSSION

The current findings reveal important patterns in biopsy indications, histopathological diagnoses, and the role of advanced diagnostic techniques. Nephrotic syndrome emerged as the predominant indication for renal biopsy, accounting for 46.99% (n = 242) of all cases. This high prevalence aligns with findings from other studies, such as Kanodia et al. [9], who reported nephrotic syndrome as the most common indication (46.2%) in their single-center study of 346 pediatric renal biopsies. Similarly, Mohapatra et al. [8] found nephrotic syndrome to be the leading indication (63.2%) in their 20-year analysis of 1,740 pediatric kidney biopsies. The consistency across these studies underscores the significant burden of nephrotic syndrome in pediatric nephrology & highlights the importance of renal biopsy in its management.

Within the nephrotic syndrome category, our study found steroid-dependent cases to be most frequent (23.5%, n = 121), followed by atypical presentations (12.23%, n = 63) and steroid-resistant cases (6.02%, n = 31). This distribution differs somewhat from that reported by Kanjilal et al. [14], who found steroid-resistant nephrotic syndrome to be the primary indication (49.18%) in their cross-sectional study of 61 children. This variance in steroid response patterns may be attributed to regional differences in patient populations, referral practices, and study periods. In our clinical setting, steroid-dependent nephrotic syndrome appears to be more prevalent than steroid-resistant cases, as reflected in our biopsy cohort. This trend underscores the importance of close monitoring and consideration of early biopsy and tailored therapeutic strategies in managing this subgroup.

Lupus nephritis emerged as the second most common indication for renal biopsy in our study, comprising 24.66% (n = 127) of cases. This finding contrasts with some other studies, such as Mohapatra et

al. [8], who reported a lower prevalence of lupus nephritis in their cohort. Our higher prevalence might reflect regional variations in disease patterns or differences in referral practices. The significant proportion of SLE cases underscores the importance of renal biopsy in managing systemic autoimmune diseases with renal involvement, as emphasized by Seshan and Salvatore [15] in their review of recurrent diseases in renal transplantation.

Other notable indications in our study included HUS with atypical or prolonged course (6.21%, n = 32), recurrent gross hematuria (6.8%, n = 35), and ARF (6.6%, n = 34). These findings highlight the diverse spectrum of renal pathologies encountered in pediatric nephrology and the crucial role of renal biopsy in their diagnosis and management. The relatively high proportion of HUS cases is particularly noteworthy and warrants further investigation into potential environmental or genetic factors contributing to its prevalence in our population.

Regarding histopathological findings by LM, our study revealed MCD as the predominant pathology in nephrotic syndrome cases (23.69%, n = 122), followed by FSGS (9.13%, n = 47) and mesangioproliferative glomerulonephritis (6.8%, n = 35). This distribution is generally consistent with other pediatric studies, such as Santangelo et al. [2], who reported MCD as the most common cause of primary glomerulonephritis in their cohort. However, our study found a higher proportion of FSGS compared to some reports, such as Souilmi et al. [16], who identified MCD in 40.2% of cases but reported a lower prevalence of FSGS. This discrepancy may reflect geographical and genetic variations in disease patterns, as well as temporal changes in the incidence of specific histopathological subtypes such as FSGS. In our population, the relatively high rate of consanguinity may contribute to the observed distribution of steroid response patterns and underlying pathology, highlighting the importance of incorporating regional genetic factors into clinical assessment and management strategies.

In SLE patients, our study found lupus nephritis class III to be most prevalent (11.07%, n = 57), followed by class IV (6.21%, n = 32) and class II (4.27%, n = 22). This distribution differs somewhat from that reported by Hu et al. [17], who found lupus nephritis to be the most common secondary glomerulonephritis but did not provide a detailed breakdown of classes. The predominance of class III lupus nephritis in our cohort is noteworthy and may have implications for treatment strategies and prognostic considerations.

Our study also highlighted the importance of EM in cases where LM results were inconclusive or required further investigation. Notably, in 13 cases (2.52%) of nephrotic syndrome with extrarenal manifestations, EM revealed Alport syndrome in all instances, despite 10 cases (1.94%) appearing normal under LM. In contrast, one case with abnormal LM (membranoproliferative) revealed subendothelial deposits, Mesangial proliferation and deposits, effaced podocytes with shed pedicles by EM. This case was diagnosed by genetic and immunological studies as autoimmune lymphoproliferative syndrome (ALPS) and DiGeorge syndrome. This finding aligns with the observations of Yamashita et al. [18], who emphasized the continued importance of EM in achieving accurate

renal biopsy diagnoses, particularly in cases of genetic disorders like Alport syndrome. Our results underscore the complementary nature of EM in providing definitive diagnoses in complex renal cases, particularly those with genetic or ultrastructural abnormalities.

The role of IF was further emphasized in our analysis of recurrent gross hematuria cases, which accounted for 30 cases (5.38%) of the EM examinations. All these cases demonstrated nonspecific abnormalities on LM, yet IF analysis revealed IgA nephropathy as the predominant underlying cause (3.69%, n = 19), followed by mesangioproliferative IgG/IgM deposits (1.75%, n = 9). Our results highlight the crucial role of IF in elucidating the etiology of recurrent gross hematuria, particularly in cases where LM fails to reveal underlying pathology. This is supported by Gurevich et al. [19], who described a case of IgA vasculitis nephropathy presenting with isolated recurrent glomerulonephritis before the appearance of purpura.

The high prevalence of IgA nephropathy in our cohort of recurrent gross hematuria cases aligns with existing literature on common causes of recurrent hematuria in pediatric populations. However, it is worth noting that our findings contrast with some studies, such as Parrey et al. [20], who found IgA nephropathy to be the most common overall diagnosis (15.7%) in their prospective study of 115 renal biopsies across all age groups. The discrepancy might be attributed to our focus on pediatric cases and the specific subset of patients with recurrent gross hematuria.

Our study's findings have important implications for clinical practice and future research. The high prevalence of steroid-dependent nephrotic syndrome suggests a need for tailored management strategies and potentially novel therapeutic approaches for this subgroup. The significant proportion of SLE cases, particularly the predominance of class III lupus nephritis, calls for increased vigilance in monitoring renal involvement in pediatric SLE patients and may inform treatment protocols.

The crucial role of EM and IF in diagnosing conditions like Alport syndrome and IgA nephropathy, even in cases with normal LM findings, underscores the importance of maintaining and potentially expanding EM and IF capabilities in pediatric nephrology centers. This aligns with the recommendations of Hull et al. [21], who advocated for the judicious use of kidney biopsy as an invasive procedure, conducted in consultation with nephrology specialists and following a comprehensive non-invasive workup.

This single-center retrospective study has several limitations. The findings may not be generalizable to other populations or healthcare settings. The retrospective nature introduces potential for selection bias and missing data. Lack of long-term follow-up data limits assessment of patient outcomes. Additionally, the reliance on medical records introduces the possibility of incomplete or inaccurate clinical information.

LIMITATIONS OF STUDY

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Additionally, the reliance on medical records introduces the possibility of incomplete or inaccurate clinical information.

RECOMMENDATIONS

Further multicenter studies with prospective nature and longer-term follow-up data should be designed in the future for accurate data collection and better assessment of patient outcomes.

ABBREVIATIONS

SLE	Systemic lupus erythematosus
EM	Electron microscopy
IF	Immunofluorescence
LM	Light microscopy
NS	Nephrotic syndrome
SDNS	Steroid-dependent NS
SRNS	Steroid-resistant NS
KDIGO	Kidney Disease Improving Global Outcomes
SD	Standard deviation
CRF	Chronic renal failure
ALPS	Autoimmune lymphoproliferative syndrome
GBM	Glomerular basement membranes
ESRD	End-stage renal disease

CONCLUSION

Renal biopsy plays a crucial role in pediatric nephrology, with nephrotic syndrome and SLE being the most common indications. MCD predominated in nephrotic syndrome cases, while class III was most prevalent in lupus nephritis. EM and IF proved invaluable in diagnosing conditions like Alport syndrome and IgA nephropathy, even when LM appeared normal.

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AUTHORS' CONTRIBUTIONS

The submitted manuscript is the work of the author & co-author.

All authors have contributed to authorship, have read, and approved the manuscript.

Conception and design of study: S. M. E.

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STATEMENTS

Consent for publication and exclusive submission

The contents and material of manuscript have not been previously reported at any length or being considered for publishing elsewhere.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and adhered to the principles of good clinical practice. Approval was obtained from the Ethics Committee of the Faculty of Medicine, Tanta University, Approval code:36264PR419/11/23.

Availability of data and material

The data and material are factual and genuine.

Conflict of Interest

The authors declare no conflict of interest.

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