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Tubulointerstitial nephropathy is the predominant finding in men in a review of more than 3000 renal biopsies over a 10-year period from Sri Lanka

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Abstract

Background Chronic kidney disease (CKD) is a significant clinical challenge in Sri Lanka. The present study presents histopathological diagnoses from native renal biopsies in Kandy District, 2011–2020.

Methods Reports of 5,014 renal biopsies principally performed at Kandy Teaching Hospital over 2011–2020 were reviewed. After exclusions for post-kidney transplant biopsies (1,572) and those without evident pathology (347), 3,095 biopsies were included. The predominant histopathological entities were grouped and categorised according to diagnosis and stratified by age and sex.

Results The main histopathological entities (all biopsies) were tubulointerstitial nephropathy (TIN) 25% ($n=760$), glomerulonephritis (GN) 15% (467), lupus nephropathy 14% (429), focal segmental glomerular sclerosis (FSGS) 10% (297), and IgA nephropathy (IgAN) 8% (242). For adult women ≥ 15 years, the main histopathological entities were lupus nephropathy 24% (325), TIN 17% (228), and GN 16% (217). For adult men ≥ 15 years, the main histopathological entities were TIN 34% (449), GN 14% (180), and IgAN 10% (125). The proportion of TIN in the present study was higher than international studies of a similar size.

Conclusion This is the largest study of renal biopsies reported from Sri Lanka to date. TIN was the most common diagnosis in adults ≥ 15 years at 25%. Notable sex differences showed TIN was the most common histopathology in men (34%) but not in women (17%). No previously published similar study of this size has found TIN as the predominant diagnosis amongst renal biopsies in men. Further research is required into the possible causes of these observations in Sri Lanka.

Clinical Trial Number.

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Keywords CKD, CKDu, Tubulointerstitial nephropathy, Sri Lanka, Chronic kidney disease of unknown aetiology, Renal biopsy

Introduction

Sri Lanka is a South Asia island country with an estimated population of 22 million in 2023 [7]. This investigation is based on the spectrum of findings from a decade (2011–2020) of native renal biopsies performed at Kandy Teaching Hospital, Sri Lanka. Kandy is the capital of Central Province, 100 km inland from the national capital Colombo, and is surrounded by extensive agricultural areas, used especially for rice cultivation. Kandy Teaching Hospital has strong links with the Medical Faculty at the adjacent University of Peradeniya Hospital, which are both public hospitals providing medical services without charge.

Prevalence and risk factors for impaired renal function in the district of Anuradhapura, Sri Lanka was assessed in a cross-sectional clustered population-representative survey in 2003–2008 of adults ≥ 19 years (n = 6,153) [1]. Participants with ≥ 1 + proteinuria (≥ 2/3 occasions) had blood taken for serum creatinine measurement from which estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) simplified equation [15]. Proteinuric-chronic kidney disease', as defined by proteinuria + 1–3 with reduced eGFR (< 60 ml/min per 1.73m^2), was present in 5.1% in Medawachchiya n = 2600 (North Central Province), 9.5% in Yatinuwara n = 709 (Central Province), and 2.3% in Hambantota n = 2844 (Southern Province).

Prevalence rates of CKDu, as measured by low estimated glomerular filtration rate (eGFR < 60 ml/min per 1.73m^2) calculated using the 'CKD EPI equation' [5, 15] from serum creatinine incorporating age and sex, in the absence of heavy proteinuria, diabetes or hypertension, has been estimated at 11% for men and 4% for women in a cross-sectional population prevalence study (n = 4,803) within affected areas in North Central Province [26].

The prevalence of CKDu in Sri Lanka has led to research into possible causes of CKD in the region and methods of prevention and control. These have involved expensive health service interventions, including early detection through population screening for renal abnormalities and diagnostic assessment as necessary (including renal biopsy), and implementation of various treatment modalities, including kidney replacement therapy [8, 12, 23, 30, 31]. Tubulointerstitial nephritis (TIN) has been reported as the predominant histopathological feature in renal biopsies from CKDu cases (n = 125, 74% male); and in 84% of cases in renal failure stage 3–4, from Anuradhapura, North Central Province, Sri Lanka 2008–2012 [27]. In a study of cases (n = 59) presenting with an acute illness with renal symptoms, and elevated serum creatinine (excluding those with known causes and/or small kidneys) from Kandy (Central Province, Sri Lanka), histopathology revealed a mixture of both acute and chronic interstitial nephropathy which, according to the authors, would imply that chronicity may be preceded by recurrent acute episodes [2].

There are numerous causes of TIN including, but not limited to, infections, autoimmune disease, environmental toxins and envenomation, among others [16]. Some renal biopsies may receive a syndromic diagnosis of CKDu when no known cause is evident without a recorded histopathological diagnosis. While TIN is associated with CKDu in Sri Lanka, TIN has not been reported as a predominant histopathological finding in most international renal biopsy studies (Table 1) [6, 13, 17, 21, 25, 28]. In Sri Lanka, the proportions of TIN reported in previous renal biopsy case series were: 4.3% in Colombo South Kalubowila [20]; 25.5% (if all TIN is included) in Nugegoda west of Colombo [24]; and 22.2% (if all TIN is included) in Kandy [4] (Table 1). Previous studies in Sri Lanka have not analysed differences in TIN by sex, despite epidemiological prevalence studies demonstrating that men are more likely to be affected by CKDu [26].

The present study is the largest investigation (n = 3,095) of native renal biopsies (2011–2020) assembled in Sri Lanka, with cases drawn in major part from a large inland agricultural region with known areas of endemic CKDu. The objectives of the present study were to: (1) describe the range and relative frequency of histopathological diagnoses, and (2) provide stratified analyses of the different patterns of histopathology for adults ≥ 15 years (by sex), and for children < 15 years.

Methods

Study design

The present study is a retrospective study of renal biopsies performed at Kandy Teaching Hospital during 2011–2020, which includes a small number (n = 52) of biopsies in children < 15 years that were performed at University of Peradeniya Hospital.

Renal biopsy

Kandy Teaching Hospital provides nephrology services for patients who present directly to the hospital with possible symptoms of renal disease, as well as routinely servicing those referred from outpatient and outreach

Table 1 Proportion of TIN in native renal biopsies, Sri Lanka and internationally

Study	Country (Region)	Years of study	Total cases	Tubulointerstitial nephropathy (n)	TIN (%)
Sri Lanka					
Present Study	Sri Lanka (Central Province) Kandy region	2011–2020	3,095	760	24.6
Muthukud et al. 2023 [20]	Sri Lanka (Western Province) Columbo South	2018–2019	140	6	4.3$p<0.001$
Pilapitiya et al. 2020 [24]	Sri Lanka (Western Province) West of Columbo	2012–2019	547	148	25.5^ P: ns
Basnayake, Wazil, et al., 2019b [4]	Sri Lanka (Central Province) Kandy region	2010–2019	2680	596	22.2^^ $p<0.04$
International					
Yim et al., 2020 [32]	Korea	2001–2023	2053		0.4
Polito et al. 2010 [25]	Brazil	1993–2007	9617		2.2
Sugiyama et al. 2013 [28]	Japan	2009–2010	4016		3.3
Li and Liu 2024 [17]	China	1979–2002	13,519		3.4
Islam et al. 2018 [13]	Bangladesh	2015	235		3.4
Mittal et al. 2020 [18]	India (North)	2006–2016	3275		5.3
Das et al. 2011 [6]	India (South)	1990–2008	1849		6.7
Mubarak et al. 2011 [19]	Pakistan	1995–2008	1793		11.6
Okpechi et al. 2011 [21]	South Africa	2000–2009	1284		5.6 – 18.0[1]

[1] Annual proportions (range). *TIN* Tubulointerstitial nephropathy

Chi square *p*-value of other Sri Lankan studies compared to present Kandy study of tubulointerstitial nephropathy of 760 cases ($n=3095$) with statistical significance at $p<0.05$. ^ (Pilapitiya 2020), ns = not significant, TIN = 148 composed of: 'chronic tubulointerstitial nephritis' (92, 62%), plus 'chronic interstitial nephritis in agricultural communities' (42, 28%), plus 'acute tubulointerstitial nephritis' (14, 19%). ^^ Basnayake et al. 4b, TIN = 596 composed of: 'tubulointerstitial disease' (382, 14%), plus 'chronic kidney disease of unknown etiology' (214, 36%)

services, and from surrounding rural hospitals and clinics. The referral pathways for renal biopsies differed over the ten-year-study period because of sporadic population screening programs, and the establishment of outreach renal clinics in areas with significant occurrence of clinical chronic kidney disease. The spatial distribution of renal biopsy cases performed at Kandy Teaching Hospital (Fig. 1) shows the intake from surrounding agricultural areas. District of residence was known for 77% ($n=2,396$) of biopsies, and of those biopsies 89% ($n=2,133$) were from districts in, or directly surrounding, Central Province (Kandy $n=757$, Matale $n=377$, Nuwara Eliya $n=251$, Badulla $n=214$, Kegalle $n=177$, Kurunegala $n=140$, Ampara $n=115$, and Polonnaruwa $n=100$).

The decision to progress to renal biopsy was at the discretion of the treating nephrologist based on clinical findings, urine analysis, serum creatinine and other blood tests, and results of renal ultrasound. Common reasons for biopsies not proceeding include small kidneys identified on ultrasound measurement (< 9 cm), lack of perceived clinical benefit where renal biopsy would not lead to a change in treatment, and patient refusal—including for socio-economic reasons, such as cost of transport and time off work to attend an appointment for the procedure.

The reasons for proceeding with renal biopsy were derived from data extracted from the Pathology Report Form (one page) and include either explicit statements of clinical indications ($n=2,047$) or were derived from the clinical information contained elsewhere on the form ($n=1,048$). The indications for renal biopsy were: nephrotic syndrome ($n=1,094$, 35%), unexplained chronic renal failure ($n=573$, 19%), unexplained proteinuria and/or haematuria ($n=638$, 21%), to plan future therapy for those previously diagnosed and treated ($n=329$, 11%), unexplained acute renal failure ($n=204$, 7%), diabetes mellitus (without haematuria) ($n=174$, 6%), unknown ($n=51$, 2%), and renal diseases in pregnancy and postpartum ($n=32$, 1%).

Preparation of biopsy

Two cores were taken from all renal biopsies: one in formal saline for routine tissue processing, and the other was a fresh sample transported in Michael's solution or with ice packing within two hours of sample collection for immunofluorescence. Formalin fixed paraffin embedded (FFPE) tissue was used for haematoxylin and eosin (H & E) stains for general histopathological evaluation and Jones' methenamine silver stains for assessment of the glomerular basement membrane. Generally, eight to twelve H & E sections were examined and if required more tissue sections were obtained. Immunofluorescence staining was performed to detect immunoglobulins and complement components, using IgG, IgA, IgM, and C3.

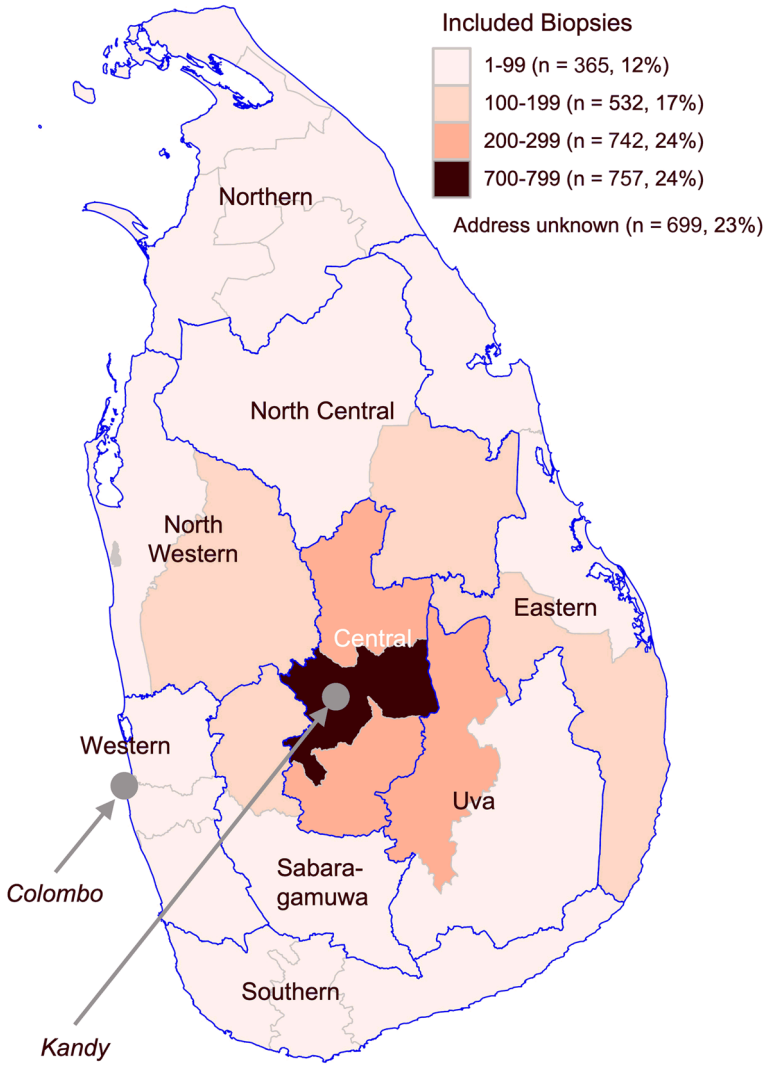

Fig. 1 Number of renal biopsies by district (grey lines) examined at Kandy Teaching Hospital, 2011–2020. (Legend for Fig. 1) Province outlines shown in blue lines. Number and proportion of biopsies represented by each coloured segment is shown in the key

Although electron microscopy was not routinely performed on all samples, it had been previously performed on a batch of cases diagnosed with chronic kidney disease of unknown aetiology (CKDu) at the University of Erlangen–Nuremberg (Germany) using FFPE tissue. This study did not identify any unique glomerular or tubular interstitial pathology for CKDu. The comprehensive approach described ensures a thorough evaluation of renal biopsies under resource constrained settings, facilitating accurate diagnosis and guiding appropriate management.

Data acquisition

Reports by pathologists who reviewed renal biopsy material for each case were abstracted onto a structured form and entered into an electronic database. Information derived from the report included specific histopathological features and a transcription of written comments and summary diagnoses by the pathologists. Demographic and residential area data were recorded. No personal identifiable data were extracted. Consequently, it was not possible to ascertain if an individual was biopsied more than once over the ten-year study period, or to follow-up individual cases. In Sri Lanka, it is usual practice for patients to take medical records home with them, so no other information was available from the hospital other than the renal biopsy report form. Completeness of data was 94% for sex and 96% for age.

Data preparation

The pathologists' written description and comments, specific histopathological features, and summary diagnoses were utilised to categorise the renal biopsies as a single predominant diagnosis. The array of diagnoses and their abbreviations reported from 52 international studies of renal biopsies (1980–2019), summarised by Muthukuda et al. [20], were taken as a guide for names, abbreviations and nosology of renal histopathological conditions. Information from published articles on particular diagnostic categories, and from the International Classification of Disease version 10 (ICD-10), were used where appropriate. Fogo et al. [9] *Fundamentals of Renal Pathology* was consulted extensively for criteria for histopathological diagnosis and for classification of diagnoses.

Certain diagnostic categories in the original pathology reports were individually reviewed in instances where glomerulonephritis (unqualified) was the sole or predominant diagnosis recorded ($n=150$), tubular injury (unqualified) was the sole or predominant diagnosis ($n=50$), multiple histopathological diagnoses were provided without selection of a predominant condition ($n=132$), CKDu was the diagnosis with or without other conditions ($n=98$), and histopathological features were reported without any diagnosis ($n=89$). In these 519 cases, comments and diagnoses by pathologists on the report form, and categorical histopathological information, were used to arrive at a probable predominant histopathological diagnosis where possible.

The histopathological findings in all 98 cases of CKDu (syndromic diagnosis) in the present study were individually reviewed using commonly accepted criteria for tubulointerstitial nephropathy. The characteristics for TIN, if present, were indicated by the pathologist on the Histopathology Report Form. These indicators compromise: (a) lymphocytic interstitial invasion and/or tubilitis (active or active); (b) tubular atrophy and/or fibrosis (interstitial, peri-glomerular, perivascular) (chronic); and (c) both together. The histopathology review of these 98 CKDu cases indicated: 92 cases of tubulointerstitial nephropathy (84 cases of tubulointerstitial nephropathy only, and 8 cases as tubulointerstitial nephropathy with an additional diagnosis).

From 5,014 renal biopsies, 1,572 post-kidney transplant biopsies were excluded. Other exclusions included 188 biopsies with no renal tissue in the biopsy core, 95 biopsies with no histopathological abnormalities (normal), and 64 biopsies with insufficient abnormalities to indicate a specific histopathological diagnosis (Fig. 2). Thus 3,095 renal biopsies were included in this study.

Data analysis

For tabulation, histopathological diagnoses were categorised according to whether they primarily affected the glomerulus, the interstitium (or adjacent structures), or were renal manifestations of systemic disease. Each category was then arranged in sub-groups according to commonly used nomenclature, and then into reportable histopathological diagnoses following Fogo et al. [9]. Counts and proportions (%) of totals were provided for each category, subgroup, and diagnosis.

Tabulations were prepared for all specific reportable histopathological diagnoses arranged into related groups as set out in Tables 2, 3, 4 and 5. The number of cases and proportion (%) of biopsies are given for specific reportable histopathological diagnoses, subgroups, and main categories. Data were stratified by (1) adults ≥ 15 years by sex, (2) children < 15 years. Chi-squared tests were conducted to compare proportions in groups within this series, and to test the statistical significance of differences in proportions of TIN compared to other similar renal biopsy studies.

Results

All cases ($n=3,095$). Following documented exclusions (Fig. 2), 47.2% of the diagnosed histopathological entities were primary glomerular lesions ($n=1,460$); tubulointerstitial and related histopathology ($n=808$) comprised 26.1%, and systemic disease with renal involvement ($n=824$) comprised 26.6% including secondary glomerular pathology (Table 2). The largest proportion of cases by individual category was accounted for by tubulointerstitial nephritis/nephropathy (TIN) ($n=760$), which comprised 24.6% of cases. This category includes cases of active (acute), chronic, and acute/active-on-chronic TIN. Other important recorded conditions included SLE 13.9%, FSGS 9.6%, IgAN 7.8%, MCD 7.3%, DN 6.6%, and membranous nephropathy (MN) 5.7%.

Women aged ≥ 15 years ($n=1,353$). Of the biopsy records for women ≥ 15 years included in analyses, 46.0% ($n=622$) of all the diagnosed histopathological entities were (primary) glomerular lesions, 18.1% ($n=245$) interstitial and related histopathology, and 35.8% ($n=484$) systemic disease with renal involvement (Table 3). The highest proportion of cases comprised SLE (24.0%), followed by TIN (16.9%). Other important recorded conditions included FSGS 10.4%, MCD 7.5%, MN 7.2%, DN 6.7%, and IgAN 6.4%.

Men aged ≥ 15 years. ($n=1,313$). Of the biopsy records for men ≥ 15 years included in analyses, 46.1% ($n=605$) of the diagnosed histopathological entities were (primary) glomerular lesions, followed by interstitial and related

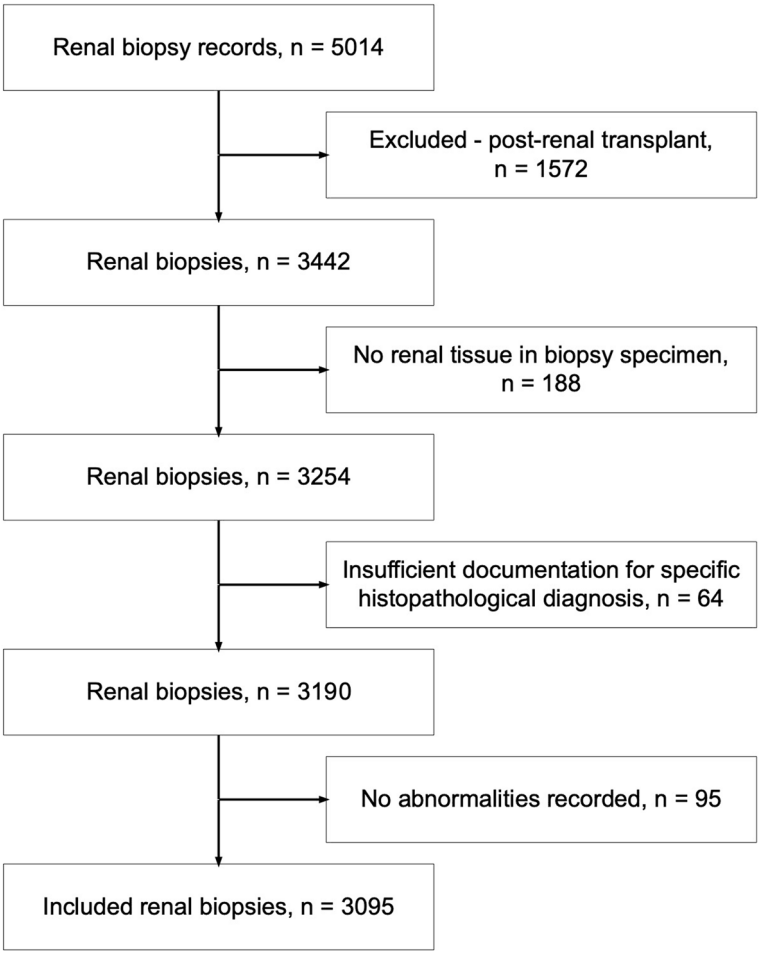

Fig. 2 Inclusion flow chart for renal biopsy record analysis, Kandy Teaching Hospital, 2011–2020

histopathology ($n=470$, 35.8%), and systemic disease with renal involvement ($n=238$, 18.1%) (Table 4). The largest proportion of cases was TIN (34.2%). Other important conditions recorded were IgAN 9.5%, FSGS 8.6%, DN 7.8%, and MCD 6.4%. The proportion of TIN was significantly higher ($p<0.001$) in men than in women.

Children < 15 years both sexes. ($n=189$). Of the biopsy records for children < 15 years included in analyses, 74.1% ($n=140$) of the diagnosed histopathological entities were (primary) glomerular lesions, 18.5% ($n=35$) were systemic disease with renal involvement, and 7.4% ($n=14$) were interstitial and related histopathology (Table 5). The most frequent individual conditions were: FSGS 14.8%, MCD 12.2%, mesangioproliferative glomerulonephritis (MesPGN) 11.6%, and SLE 10.1%. Other important conditions were IgAN 9.0%, proliferative glomerulonephritis (PGN) 7.9%, glomerulonephritis (GN n.o.s.) 7.9%, and TIN 6.7%.

Comparison of TIN to other renal biopsy studies

For adults ≥ 15 years of both sexes ($n=2{,}666$) in the present study, 677 (25.4%) were recorded as TIN**,** which is similar in magnitude but statistically significantly higher ($p=0.008$) than 22.2% (including all TIN) in the previous Kandy study (2010–2019) including all probable TIN = 596 cases for ages ≥ 12 years ($n=2680$) (because of the large numbers in both studies) [4]. The proportion of TIN in the present study is not statistically significantly different ($p=0.44$) from 25.5% (including all probable TIN = 148 cases) in the Nugegoda study (west of Colombo) of ages ≥ 12 years ($n=547$) [24]. The proportion of TIN in the present study is statistically significantly higher ($p<0.001$) than the 2.9% from 4 cases of TIN in the Kalubowila study ($n=140$) from Colombo south of ages ≥ 16 years [20]. Proportions of TIN reported in similarly sized renal biopsy case series from Korea (TIN = 0.04%) [32], India (5.3%) [18], and Pakistan (11.6%) [19] were all significantly lower than in the present study ($p<0.001$).

Table 2 Histopathology of all native renal biopsies, Kandy, Sri Lanka, 2011–2020

	n	%	n	%	n	%
1. PRIMARY GLOMERULAR NEPHROPATHIES					1,460	**47.17**
Glomerulonephritis			467	**15.09**		
Glomerulonephritis GN n.o.s	126	4.07				
Crescentic glomerulonephritis CresGN n.o.s	55	1.78				
Proliferative glomerulonephritis PG n.o.s	110	3.55				
Membranous glomerulonephritis/nephropathy MN n.o.s	176	**5.69**				
Membranoproliferative glomerulonephritis MPGN			76	2.46		
Membranoproliferative glomerulonephritis n.o.s	13	0.42				
Mesangiocapillary glomerulonephritis (synonymous with MPGN)	63	2.04				
Mesangioproliferative glomerulonephritis			373	**12.05**		
Mesangioproliferative glomerulonephritis MesPGN n.o.s	113	3.65				
Mesangioproliferative glomerulonephritis specific immune deposits						
IgA nephropathy IgAN	242	**7.82**				
IgM nephropathy IgMN	15	0.48				
C3 complement glomerulonephritis C3GN	3	0.10				
Minimal change disease MCD	226	**7.30**	226	**7.30**		
Glomerular sclerosis			318	**10.27**		
Glomerulosclerosis n.o.s. GS	21	0.68				
Focal segmental glomerular sclerosis FSGS	297	**9.60**				
2. RENAL INTERSTITIUM, CORTEX AND MEDULLA					808	**26.10**
Tubulointerstitial nephropathy TIN	760	**24.56**	760	**24.56**		
Other histopathological entities			48	1.55		
Acute tubular Injury						
Acute tubular injury without necrosis ATInonec	27	0.87				
Acute tubular necrosis ATN	9	0.29				
Pyelonephritis	11	0.36				
Acute cortical necrosis	1	0.03				
3. SYSTEMIC DISEASE WITH RENAL INVOLVEMENT^					824	**26.62**
Generalised diseases			246	**7.95**		
Diabetic nephropathy DN	205	**6.62**				
Hypertensive nephropathy HTN	11	0.36				
Amyloidosis	25	0.81				
Hereditary nephritis, including Alport's syndrome	5	0.16				
Neoplasm			8	0.26		
Multiple myeloma MM. Bence Jones protein	8	0.26				
Systemic immune-related syndromes			570	**18.42**		
Lupus nephropathy, Systemic lupus erythematosus SLE	429	**13.86**				
Henoch-Schönlein purpura nephropathy HSPN	34	1.10				
Vasculitis incl with anti-neutrophil cytoplasmic antibodies (ANCA)	45	1.45				
Pauci-immune glomerulonephritis PIGN	17	0.55				
Necrotising glomerulonephritis NecGN	36	1.16				
Other immune-related conditions*	9	0.29				
Other condition(s)*	3	0.10	3	0.10	3	0.10
Total	3,095	100	3,095	100	3,095	100

n.o.s. not otherwise specified

^Systemic disease with kidney involvement includes secondary glomerular nephropathies. ≥ 5% in **Bold**

* Includes the following entities: *Other immune-related conditions:* Haemolytic uraemic syndrome HUS/Thrombotic microangiopathy TMA $n = 2$; Cryoglobulinaemia-associated membranoproliferative glomerulonephritis $n = 1$; Systemic sclerosis $n = 1$; Anti-glomerular basement membrane disease $n = 3$; Wegner's granulomatosis $n = 2$. *Other conditions*: Pre-eclampsia $n = 2$; Renal tuberculosis Renal TB $n = 1$

Table 3 Histopathology of renal biopsies, women aged ≥ 15 years, Kandy, Sri Lanka, 2011–2020

	n	%	n	%	n	%
1. PRIMARY GLOMERULAR NEPHROPATHIES					622	**45.97**
Glomerulonephritis			217	**16.04**		
Glomerulonephritis GN n.o.s	56	4.14				
Crescentic glomerulonephritis CresG n.o.s	22	1.63				
Proliferative glomerulonephritis PG n.o.s	41	3.03				
Membranous glomerulonephritis/nephropathy MN n.o.s	98	**7.24**				
Membranoproliferative glomerulonephritis MPGN			23	1.70		
Membranoproliferative glomerulonephritis n.o.s	5	0.37				
Mesangiocapillary glomerulonephritis (synonymous with MPGN)	18	1.33				
Mesangioproliferative glomerulonephritis			133	**9.83**		
Mesangioproliferative glomerulonephritis MesPGN n.o.s	40	2.96				
Mesangioproliferative glomerulonephritis specific immune deposits						
IgA nephropathy IgAN	86	**6.36**				
IgM nephropathy IgMN	6	0.44				
C3 complement glomerulonephritis C3GN	1	0.07				
Minimal change disease MCD	102	**7.54**	102	**7.54**		
Glomerular sclerosis			147	**10.86**		
Glomerulosclerosis n.o.s. GS	7	0.52				
Focal segmental glomerular sclerosis FSGS	140	**10.35**				
2. RENAL INTERSTITIUM, CORTEX AND MEDULLA					245	**18.11**
Tubulointerstitial nephropathy TIN	228	**16.85**	228	**16.85**		
Other histopathological entities			17	1.26		
Acute tubular Injury						
Acute tubular injury without necrosis ATInonec	10	0.74				
Acute tubular necrosis ATN	3	0.22				
Pyelonephritis	4	0.30				
3. SYSTEMIC DISEASE WITH RENAL INVOLVEMENT^					484	**35.77**
Generalised diseases			101	**7.46**		
Diabetic nephropathy DN	90	**6.65**				
Amyloidosis	10	0.74				
Hereditary nephritis, including Alport's syndrome	1	0.07				
Neoplasm			4	0.30		
Multiple myeloma MM. Bence Jones protein	4	0.30				
Systemic immune-related syndromes			379	**28.01**		
Lupus nephropathy, Systemic lupus erythematosus SLE	325	**24.02**				
Henoch-Schönlein purpura nephropathy HSPN (IgA)	12	0.89				
Vasculitis incl with Anti-neutrophil cytoplasmic antibodies (ANCA)	18	1.33				
Pauci-immune glomerulonephritis PIGN	6	0.44				
Necrotising glomerulonephritis NecGN	17	1.26				
Other immune-related conditions. See below	1	0.07				
Other condition(s)*	2	0.15	2	0.15	2	0.15
Total	1,353	100	1,353	100	1,353	100

n.o.s. not otherwise specified

^Systemic disease with kidney involvement includes secondary glomerular nephropathies. ≥ 5% in **Bold**

* *Includes the following entities:* Other conditions: Pre-eclampsia, *n* = 1; Renal tuberculosis Renal TB *n* = 1

Discussion

This retrospective analysis of 3,095 native renal biopsies performed at Kandy Teaching Hospital between 2011 and 2020 aimed to characterise the predominant histopathological all age findings, and to examine differences in diagnoses in adults ≥ 15 years by sex, and

Table 4 Histopathology of renal biopsies, men aged ≥ 15 years, Kandy, Sri Lanka, 2011–2020

	n	%	n	%	n	%
1. PRIMARY GLOMERULAR NEPHROPATHIES					605	**46.08**
Glomerulonephritis			180	**13.71**		
Glomerulonephritis GN n.o.s	48	3.66				
Crescentic glomerulonephritis CresG n.o.s	21	1.60				
Proliferative glomerulonephritis PG n.o.s	50	3.81				
Membranous glomerulonephritis/nephropathy MN n.o.s	61	4.65				
Membranoproliferative glomerulonephritis MPGN			40	3.05		
Membranoproliferative glomerulonephritis n.o.s	4	0.30				
Mesangiocapillary glomerulonephritis (synonymous with MPGN)	36	2.74				
Mesangioproliferative glomerulonephritis			176	**13.40**		
Mesangioproliferative glomerulonephritis MesPGN n.o.s	43	3.27				
Mesangioproliferative glomerulonephritis specific immune deposits						
IgA nephropathy IgAN	125	**9.52**				
IgM nephropathy IgMN	6	0.46				
C3 complement glomerulonephritis C3GN	2	0.15				
Minimal change disease MCD	84	**6.40**	84	**6.40**		
Glomerular sclerosis			125	**9.52**		
Glomerulosclerosis n.o.s. GS	12	0.91				
Focal segmental glomerular sclerosis FSGS	113	**8.61**				
2. RENAL INTERSTITIUM, CORTEX AND MEDULLA					470	**35.80**
Tubulointerstitial nephritis TIN	449	**34.20**	449	**34.20**		
Other histopathological entities			21	1.60		
Acute tubular injury						
Acute tubular injury without necrosis ATInonec	10	0.76				
Acute tubular necrosis ATN	3	0.23				
Pyelonephritis	7	0.53				
Acute cortical necrosis	1	0.08				
3. SYSTEMIC DISEASE WITH RENAL INVOLVEMENT^					238	**18.13**
Generalised diseases			121	**9.22**		
Diabetic nephropathy DN	102	**7.77**				
Amyloidosis	7	0.53				
Hereditary nephritis, including Alport's syndrome	2	0.15				
Hypertensive nephropathy HTN	10	0.76				
Neoplasm			4	0.30		
Multiple myeloma MM. Bence Jones protein	4	0.30				
Systemic immune-related syndromes			113	**8.61**		
Lupus nephropathy, Systemic lupus erythematosus SLE	53	4.04				
Henoch-Schönlein purpura nephropathy HSPN (IgA)	9	0.69				
Vasculitis incl with Anti-neutrophil cytoplasmic antibodies (ANCA)	24	1.83				
Pauci-immune glomerulonephritis PIGN	7	0.53				
Necrotising glomerulonephritis NecGN	15	1.14				
Other immune-related conditions*	5	0.38				
Total	1,313	100	1,313	100	1,313	100

n.o.s. not otherwise specified

^Systemic disease with kidney involvement includes secondary glomerular nephropathies. ≥ 5% in **Bold**

* *Includes the following immune related syndromes*: Wegner's granulomatosis *n* = 1; Cryoglobulinaemia-associated membranoproliferative glomerulonephritis *n* = 1; Systemic sclerosis *n* = 1; Anti-glomerular basement membrane disease *n* = 2

Table 5 Histopathology of renal biopsies, children < 15 years, Kandy, Sri Lanka, 2011–2020

	n	%	n	%	n	%
1. PRIMARY GLOMERULAR NEPHROPATHIES					140	**74.07**
Glomerulonephritis			39	**20.63**		
Glomerulonephritis GN n.o.s	15	**7.94**				
Crescentic glomerulonephritis CG n.o.s	6	3.17				
Proliferative glomerulonephritis PG n.o.s	15	**7.94**				
Membranous glomerulonephritis/nephropathy MN n.o.s	3	1.59				
Membranoproliferative glomerulonephritis MPGN			7	3.70		
Membranoproliferative glomerulonephritis n.o.s	1	0.53				
Mesangiocapillary glomerulonephritis (synonymous with MPGN)	6	3.17				
Mesangioproliferative glomerulonephritis			41	**21.69**		
Mesangioproliferative glomerulonephritis MesPGN n.o.s	22	**11.64**				
Mesangioproliferative glomerulonephritis specific immune deposits						
IgA nephropathy IgAN	17	**8.99**				
IgM nephropathy IgMN	2	1.06				
Minimal change disease MCD	23	**12.17**	23	**12.17**		
Glomerular sclerosis			30	**15.87**		
Glomerulosclerosis n.o.s. GS	2	1.06				
Focal segmental glomerular sclerosis FSGS	28	**14.81**				
2. RENAL INTERSTITIUM, CORTEX AND MEDULLA					14	**7.41**
Tubulointerstitial nephritis TIN	13	**6.88**	13	**6.88**		
Other histopathological entities			1	0.53		
Acute Tubular Necrosis ATN	1	0.53				
3. SYSTEMIC DISEASE WITH RENAL INVOLVEMENT^					35	**18.52**
Generalised diseases			2	1.06		
Hereditary Nephritis, including Alport's syndrome	2	1.06				
Systemic immune-related syndromes			33	**17.46**		
Lupus Nephropathy, Systemic Lupus Erythematosus SLE	19	**10.05**				
Henoch-Schönlein Purpura nephropathy HSPN (IgA)	8	4.23				
Haemolytic Uraemic Syndrome / Thrombotic Microangiopathy	2	1.06				
Pauci-immune glomerulonephritis PIGN	1	0.53				
Necrotising Glomerulonephritis NecGN	3	1.59				
Total	189	100	189	100	189	100

n.o.s. not otherwise specified. ^Systemic disease with kidney involvement includes secondary glomerular nephropathies. ≥ 5% in **Bold**

children < 15 years. Although the majority of documented histopathological entities were primary glomerular lesions (47%) of all biopsies, there were important differences between adults ≥ 15 years of each sex, and with children < 15 years compared to adults. In a quarter of all biopsies the main histopathological entity was TIN (25%), however, in adult males TIN was 34% ($n = 448$) compared to adult females 17% ($n = 228$). In children < 15 years TIN was 7% ($n = 13$).

In similar studies from other parts of Sri Lanka, TIN has been reported to vary from 4% in Colombo South Teaching Hospital (Kalubowila) ($n = 140$, 56% female) [20], to 22% in Kandy ($n = 2680$) [4], and 26% in Nugegoda (west of Colombo) ($n = 771$, 67% male) if all related TIN categories are included [24]. The present study in Kandy ($n = 3{,}095$) found the proportion of TIN to be statistically significantly higher ($p < 0.001$) than in Kalubowila (Columbo south), but not significantly different from that in the Nugegoda study ($p > 0.05$). Although the magnitude of the proportions of TIN in the present Kandy study 2011–2020 ($n = 3095$) at 25% is not substantially different from the 22% probable TIN in the previous Kandy study 2010–2019 ($n = 2680$), because of the large numbers the difference was statistically significant at $p < 0.04$.

Stratification of TIN by sex was not included in previous Sri Lanka biopsy studies, which also did not include children < 12 years [4, 24]. The breakdown by sex in the present study highlights a significantly higher proportion of TIN in men compared to women. The sex difference in

proportions of TIN is likely influenced by more frequent occupational exposure to putative causes through farming activities in men than women, and the higher occurrence of lupus nephropathy in women than men.

In international renal biopsy studies, the proportion of tubulointerstitial nephritis has varied from 0.4% of total cases in Korea [32] to 18% of cases in South Africa [21] (Table 1). Protocols for referral for renal biopsy may differ between centres and countries, which may impact direct comparisons, but the evidence suggests that the proportion of TIN found in the present study is higher than renal biopsy studies from other countries. The findings of a male predominance in TIN have been reported in studies of CKDu in Sri Lanka [14] and in Nicaragua [10, 29]. The higher proportion of TIN found in Sri Lanka remains unexplained compared to international findings and further research is required into the causes.

Published studies from south India suggest occurrence of endemic interstitial nephropathy in areas of Tamil Nadu and Andhra Pradesh, although the report of 'Tondaimandalam nephropathy' is a clinical study of CKDu cases with no histopathology from renal biopsy, and 'Uddanam Endemic Nephropathy' is based on a pathology series of 6 cases (with raised serum creatinine) of chronic tubulointerstitial nephritis on renal biopsy [11, 22].

Strengths of the present study include the large number of renal biopsies ($n=3,095$) over a ten-year period, which is the largest study of renal biopsy records in Sri Lanka. The size is comparable to large similar studies from other countries over multi-year periods (Table 1), including in Korea ($n=2053$) [32], India ($n=3275$) [18], and Pakistan ($n=1793$) [19]. The present study shows a statistically significant ($p<0.001$) higher proportion of TIN compared to the similarly sized Korean, Indian and Pakistan studies. Other strengths include: coverage of extensive agricultural areas in central Sri Lanka where endemic CKDu has been observed; the examination of renal biopsies at Kandy Teaching Hospital allied to the Medical Faculty of the University of Peradeniya; and the high completion rate of 95% for age and sex in the data.

Inevitable limitations of studies of renal biopsies are that they capture only a part of those with renal disease since their inclusion depends upon the vagaries of: clinical presentation or selection for screening, access to nephrologists and hospital care, clinical decisions concerning the need for biopsy, and patient consent. Renal biopsy studies can also be used for detailed study of particular clinical syndromic presentations of kidney disease, such as, acute or chronic kidney failure, chronic kidney failure of unknown cause (CKDu) [27], or nephrotic syndrome [3].

In summary, the proportion of TIN was considerably higher than those reported in most published renal biopsy studies to date. The proportion of TIN in men (34%) was double that found in women (17%), a sex difference which has not been reported in other similar studies. These findings warrant further and intensive research to understand potential causes.

Abbreviations

GN	Glomerulonephritis
CresGN	Crescentic glomerulonephritis
PGN	Proliferative glomerulonephritis
PIGN	Pauci-immune glomerulonephritis
NecGN	Necrotising glomerulonephritis
MN	Membranous glomerulonephritis/nephropathy
MPGN	Membrano proliferative glomerulonephritis
MCGN	Mesangio capillary glomerulonephritis
MesPGN	Mesangio proliferative glomerulonephritis
IgAN	IgA nephropathy
IgMN	IgM nephropathy
C3GN	C3 complement glomerulonephritis
MCD	Minimal change disease
GS	Glomerulosclerosis
FSGS	Focal segmental glomerular sclerosis
TIN	Tubulointerstitial nephritis
ATInonec	Acute tubular injury without necrosis
ATN	Acute tubular necrosis
DN	Diabetic nephropathy
HTN	Hypertensive nephropathy
MM	Multiple myeloma
HSPN	Henoch-Schönlein purpura nephropathy
SLE	Systemic lupus erythematosus
HUS	Haemolytic uraemic syndrome
TMA	Thrombotic microanigopathy
Renal TB	Renal tuberculosis

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Authors' contributions
JP, RT, NN and MF conceptualized and designed the study. Collection of renal specimens and histopathological examination were performed by NN, AW, NR, SW, ST. Data collection was undertaken by SP. Data entry into the database was undertaken by JP. Data analyses were done by JP, SM, RT and CL. Guidance on interpretation of data was provided by JK and ZE. Manuscript writing was undertaken by JP, RT, CL, NO and SM. All authors contributed to the review of the manuscript and approved the final manuscript.

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Availability of data and materials
Data may be obtained upon written request to the corresponding author subject to ethics approval.

Declarations

Ethics approval and consent to participate
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Consent for publication
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Competing interests
The authors declare no competing interests.

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